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ANNALS OF INTERNAL MEDICINE

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JULY, 1936

NUMBER 1

THE TREATMENT OF PNEUMONIA

By RUFUS COLI, M.D. *New York, N. Y.*

THIRTY years ago Dr. Osler wrote, "Pneumonia is a self-limited disease, which can neither be aborted nor cut short by any means at our command." When I went to the Rockefeller Institute shortly afterwards, I said to myself, "Here, at least, is a wide open field. This is the most serious acute infectious disease with which physicians have to deal. Is it possible that nothing can be done to decrease the frightful mortality due to this malady? At any rate, we can attempt to obey St. Paul's injunction, 'Prove all things, hold fast that which is good.'" From that time to this, my associates and I have tested many new things, and while we have tried to hold fast to that which is good, we may have failed to see the nuggets scattered among the rubbish, and time and the work of others may show that certain methods which I may reject today, or condemn with faint praise, if properly applied, are of value.

Before any judgment may be drawn regarding the value of any form of treatment, clear-cut definition must be made of the condition in which the therapy is applied. It is useless to speak of the value of any form of treatment in pneumonia unless all the cases are sufficiently alike that we may consider this disease a clinical entity. The term "pneumonia," however, is now applied to all those conditions in which there occurs an acute exudative inflammation involving the parenchyma of the lungs. But that leaves us about where we were less than a hundred years ago, in our conception of acute abdominal diseases, when typhoid, paratyphoid, appendicitis, peritonitis, dysentery, and diarrhea were all spoken of as "inflammation of the bowels." The development of pathological anatomy was followed by the grouping of all cases of pneumonia into two forms, one, in which complete lobes are involved, lobar pneumonia, and second, those in which the involvement is irregular and patchy, bronchopneumonia. But today even the pathologist, with the tissues before him, frequently hesitates to say whether the condition from which the patient suffered should be called lobar or bronchopneumonia.

* Read at the Detroit meeting of the American College of Physicians, March 5, 1936.
From the Hospital of the Rockefeller Institute for Medical Research, New York.

From the standpoint of therapy this anatomical differentiation of cases has been of little value, and so far as therapy directed toward overcoming the specific etiologic agents is concerned, it is almost worthless. However, the term "lobar pneumonia" is today well established in medical literature. It would be impossible, even if desirable, to supplant it, but it adds very much to its usefulness if it be limited to cases in which pneumococcus is demonstrated to be the etiologic agent. All the other cases of pneumonia, due to streptococci, staphylococci, etc., may be included under the term "atypical pneumonia," also not a good term, but I know of none better. Today, I shall confine my attention to acute lobar pneumonia, that is, acute pneumococcus infection of the lungs.

For specific treatment, an etiologic diagnosis is essential, but before this is made it must first be determined whether or not the patient is really suffering from pneumonia, and this should be decided as early as possible.

At present, most physicians wait for the appearance of physical signs of consolidation before making a diagnosis. Patient after patient has been sent into our hospital with the statement that he has been suffering with severe symptoms for three, four, five, or even more days, but that the signs of pneumonia have just appeared.

The truth of the matter is that evidence of consolidation is not necessary for the diagnosis of pneumonia. To the experienced observer the symptoms of the onset of this disease are, in most cases, definite and unmistakable. In almost all cases the person who has a chill, fever over 102° , cough, pain in the side, rapid respirations, and, above all, who is expectorating sputum which is bloody or even only slightly tinged with blood, has pneumonia. Even in persons who have suffered from cough or mild upper respiratory infections before the onset, as is the history in 60 per cent of the cases, the appearance of the more serious pulmonary infection is, in most instances, clearly indicated by the more or less sudden appearance of the symptoms I have mentioned. We physicians have made the diagnosis of pneumonia too difficult, and it is much less harmful to make an occasional mistake than to live in fancied security for days until the time when specific treatment would be useful is passed. Most cases *threatened* with pneumonia have pneumonia.

The determination of the etiologic agents in all cases of pneumonia involves difficulties, but in my opinion they are not unsurmountable. Fortunately, laboratory methods are now available by means of which this can be accomplished with little delay. By the so-called Neufeld method, all that is necessary is to treat the sputum with rabbit immune sera of the various types. If, for instance, the organisms are of Type I, swelling of the capsules occurs in Type I serum and in sera of no other types. In probably the majority of cases of pneumonia, the matter is really as simple as this, but not in all, and the physician as well as the bacteriologist must take some trouble and pains. The examination of sputum should be considered an

emergency procedure It should not be delayed until the next morning or until other work is out of the way

SERUM THERAPY

Twenty-two years ago at the Hospital of the Rockefeller Institute, we began the treatment of lobar pneumonia with specific immune serum This was undertaken because evidence derived from animal experimentation indicated that the procedure was theoretically sound During the intervening years the efficacy of serum treatment in animals has been abundantly demonstrated Blake and Cecil have shown that monkeys suffering from experimental pneumonia may be cured by the injection of homologous antipneumococcus horse serum, even after the pneumonic process is well established, and Goodner has demonstrated the curative value of immune serum in the much more susceptible rabbits even when the administration of serum is delayed as long as 72 hours following infection

But demonstrations in animals are not sufficient We must know by actual experience whether or not serum treatment in man is effective Our first observations in man gave to me very convincing evidence that if sufficient serum be used, and used promptly, true curative effects were obtained in cases due to Type I pneumococci The evidence was less convincing in the cases due to Type II organisms

During these years we have treated with serum all cases of Type I pneumonia entering the Hospital of the Rockefeller Institute, except, first, an inconsiderable number of children, most of whom recover without serum, second, patients who were moribund on admission and died before treatment could be instituted, and, third, patients who on admission were manifestly in the stage of recovery Until two years ago, whole serum in doses of 100 c c was administered, during the past two years concentrated serum has been used As early as 1915, Avery determined which fraction of the serum contained the immune principles, and demonstrated how concentration of the serum might be accomplished We delayed employing concentrated serum, however, for many years, even after improved methods for concentrating the serum were devised by Felton and others, for the following reasons In the first place, concentration adds materially to the expense of an already very expensive procedure, since in all methods of concentration a large loss of immune substances inevitably occurs Concentrated serum contains nothing which the unconcentrated does not contain In the second place, in our opinion the methods first employed for standardization of the concentrated serum gave entirely misleading information regarding its actual strength With the methods first proposed, it was claimed that a concentration of twenty or more times that of the original serum had been obtained and doses of 5 c c of the concentrated serum were considered adequate Our own observations and experience taught that this was impossible Specific treatment in this serious disease is not of the type of a teaspoonful

three times a day before meals. One cannot discuss whether serum treatment, even in Type I pneumonia, is or is not effective. All depends on how it is used. Even at present, its employment is still a complicated procedure, and for its successful use more knowledge is required than that which is given on the wrappers supplied by the commercial houses.

Several years ago, when the New York State Board of Health was able to supply serum concentrated from good effective serum, and not from weak serum which would otherwise be useless, and when we could be sure that it was standardized by a satisfactory method, we began using this, not in doses of a few c c, but in 15 to 30 c c doses. That is, it has been possible to concentrate the serum three to five times. Using the determination of strength employed by the New York State Board of Health, the doses we have used contain 90,000 units.

The greater ease of administration of the concentrated serum is obvious. In addition, most observers feel that the frequency of immediate reactions is less. This, however, is not certain. Anaphylactic reactions may occur with small amounts of serum as well as with large. Febrile reactions depend very much upon the care with which sera are prepared. Certain lots of unconcentrated sera give febrile reactions in a large proportion of cases, others rarely. In our experience, however, using both concentrated and unconcentrated serum from the same source, the febrile reactions with the concentrated serum have been notably less than with the whole serum. Probably the greatest value in using the concentrated serum consists in a decrease in frequency and severity of the symptoms of serum disease. These symptoms occur, however, with either the concentrated or unconcentrated serum, in at least half of the cases, seven to ten days following the administration of the serum. With present knowledge there is no way in which these unpleasant but harmless symptoms may be completely avoided.

In our clinic 462 cases of Type I pneumonia have now been treated with immune serum. Its value has been judged by the apparent effect on the symptoms, the rapid appearance of immune substances in the blood, the fact that following its administration bacteria disappear from the blood, and on the mortality rate in the patients treated.

Of the 462 treated cases, 48 died, a mortality rate of 10.5 per cent. Since, during the same period, the mortality rate in cases of pneumonia not due to Type I pneumococci has remained at about the same level as that of other hospitals, it seems that the low rate in Type I cases is definitely dependent upon the serum treatment employed.

All cases admitted have been treated as soon as the diagnosis was made. This is of importance because some of those employing serum have recommended that it be used only in cases that can be treated as early as the third or possibly the fourth day. It is true that the effectiveness of the serum is apparently greater the earlier in the disease it is used, but our experience indicates that no patient, however late he is seen, should be deprived of the benefits of this measure. In this series the mortality rate in cases

treated during the first three days was 48 per cent, in those treated on the fourth day or earlier, 82 per cent, on the fifth day or earlier, 86 per cent, and in those treated after the fifth day, 19.5 per cent

In general, our earliest conclusions regarding the value of Type II serum have been confirmed—namely, that it is not sufficiently effective to justify its general use. Sera for treatment in cases due to pneumococci of some of the higher types have now been prepared, and the results with some of them seem to be good, but the experience as yet is not sufficiently large to permit conclusions to be drawn. It is not impossible that with improvements in methods even Type II serum may be made useful. Type III pneumococci differ from the others in their immunological properties, and it is probable that if specific treatment in cases due to these organisms can be developed it will have to be based on different principles. The complaint is sometimes made that, after all, serum treatment is possible in only a part of the cases of pneumonia, and attempts are made to treat all cases either with Type I sera or with so-called polyvalent sera. Type I pneumonia, however, in this country probably causes 25,000 deaths every year, more than twice as many as were ever due to typhoid, even when it was most prevalent. Type I pneumonia should be looked upon as a specific infectious disease, as specific as is typhoid fever, and be treated as such.

From our experience, therefore, Type I serum should be given as early as possible and in large amounts, and the doses should be repeated every four or five hours until definite effects are seen in the fall of temperature, decrease in pulse and respiratory rates, and improvement in the other signs of intoxication. It is better to give too much than too little. Skin tests with soluble specific substance, as proposed by Francis, are useful in determining when sufficient serum has been given, but the observer must have had considerable experience in order to rely on this method alone.

Much stress has been laid upon the possible dangers of violent reactions. There are some risks, but it is now possible to guard against them. That disastrous results did not occur when we first began using very large amounts of serum intravenously, when we did not know the dangers or how to guard against them, shows that the dangers are not too great. By making preliminary tests for serum sensitiveness, by proceeding very slowly in the first injection, and by prompt use of adrenalin in case any symptoms occur, the possibilities of serious serum complications are almost entirely avoided.

CHEMOTHERAPY

The only other form of therapy at present employed in overcoming the infectious agent consists in the use of chemotherapeutic agents, such as optochin and other quinine derivatives. While studies made by Morgenroth and others have demonstrated that in mice infected with pneumococci definite curative effects may be obtained, experimental and clinical studies made in our clinic and elsewhere have shown that in man, in order to obtain

sufficient concentration of the drugs to be effective, such large doses must be employed that toxic effects, notably amblyopia, occur, and that the use of these drugs in human therapy is therefore unjustifiable

It hardly seems necessary to discuss vaccine treatment, since at present it has no experimental or theoretical justification

GENERAL MEASURES

Apart from specific therapy, however, the physician is not entirely without weapons in the struggle with pneumonia, though it must be admitted that they are not very powerful ones

Possibly the most important measure is rest. In the last analysis it is always the patient himself that must overcome the infection, even with the aid of serum, and everything that conserves the patient's strength is of importance. The first advice to be given to patients with pneumonia, even though they do not appear very ill at the onset, is to keep as quiet as possible. The second important point is to reassure them. Fear is as serious an element in the battle with pneumonia as we are told that it is in a financial depression.

MORPHINE

Something may be accomplished with drugs in allaying restlessness, but the ideal drug for this purpose is still to be sought. Formerly I was of the opinion that morphine was of much value in the treatment of pneumonia, and my clinical experience still leads me to believe that, especially in patients with severe pleural pain, in the early stages of the disease, there is no other drug which will so satisfactorily allay the general restlessness and permit the conservation of strength and energy. In view of the more accurate studies of Davis made in our clinic, however, we have become much more conservative in its use. It was found that in most cases following its administration there occurred not only a slowing in respiratory rate, but also a diminution in pulmonary ventilation and a decrease in oxygen saturation of the arterial blood. These changes were not striking, however, and it was found that when the depth of respiratory movements was diminished on account of the pain, the relief following the administration of morphine might result in actual increase in the pulmonary ventilation. In cases of extensive pulmonary involvement with diffuse moist râles, however, the administration of morphine at times resulted in a marked degree of anoxemia.

OXYGEN THERAPY

Probably the most striking functional change seen in pneumonia is rapid, shallow breathing, with deficient saturation of the arterial blood, as indicated by cyanosis. So far no satisfactory specific method for increasing the pulmonary ventilation has been found. The usefulness of breathing air containing an increased percentage of carbon dioxide has been much recom-

mended, but in our experience this procedure has not given significant therapeutic results. While the anoxemia bears some relation to the rapid and shallow breathing, it is probably related in greater measure to the impairment of the respiratory surface of the lungs, especially where there is much fluid exudate.

Twenty years ago, although the inhalation of oxygen in various pathological conditions had been long employed, the value of this procedure was much in doubt, and certain physiologists even claimed that on theoretical grounds its administration was useless. To attempt to settle this question, there was built in the Hospital of the Rockefeller Institute a chamber in which the oxygen content of the air could be regulated, and in which patients suffering from pneumonia could be treated. The results in the relief of cyanosis were so striking that since then numerous chambers in various hospitals have been constructed, and many other devices for increasing the oxygen content of the air breathed by the patient have been designed.

So far as simplicity of operation, comfort of the patient, and convenience as regards nursing are concerned, there can be no doubt that the chamber is *par excellence* the method of choice. But the initial expense is great, and chambers are not generally available. Tents have now been perfected so that in them it is possible to maintain a constant atmosphere at an even temperature almost as satisfactorily as in the oxygen chamber. The nasal catheter method is useful, but is to be recommended only when no other method is available. Recently a very ingenious and simple method of administering oxygen has been devised by Dr. Burgess of Providence. This consists merely of a box, open at the top, lined on the sides and bottom by a rubber bag attached by clamps to the upper edges of the box. At the front is an opening in the rubber bag through which the head is thrust, the edges of the opening fitting tightly about the neck. In the bag near the bottom are openings for tubes through which oxygen is allowed to flow continuously. The oxygen diffuses only slowly upward, so that with a flow of four to six liters per minute the air in the bag at the level of the patient's mouth and nose can be kept constantly at 40 to 50 per cent of oxygen. With a satisfactory cooling system, the apparatus can be employed continuously without discomfort to the patient.

In our earlier employment of the oxygen chamber we determined whether a patient should be treated by this method or not by making actual measurements of the degree of oxygen unsaturation in the arterial blood. It has been found, however, that the degree of cyanosis present is a sufficiently accurate indicator.

Our custom is to maintain an atmosphere in the chamber containing 40 to 50 per cent oxygen, usually 40 per cent. Others advise higher concentrations, but it must always be borne in mind that very high oxygen atmospheres are toxic. There seems little use in increasing the oxygen to a level higher than that necessary to relieve the cyanosis. It is not likely that placing the patient in the chamber for short periods of time is of any value. Having

once placed a patient in the chamber, it is our usual custom to keep him there until the acute intoxication is over, and then to bring about the change to usual atmospheric conditions very gradually

It is very difficult to evaluate the actual benefit derived from the use of oxygen. While, by an occasional patient, much subjective relief is obtained, in most instances this is not evident. The immediate effect on the character and frequency of respirations is not so great as certain of the reports would lead us to expect. What the effect may be on the final outcome cannot be stated at present with any degree of accuracy. Contrary to the statements of other enthusiastic observers, I can only say that our mortality in cases not treated with serum has not notably diminished since the introduction of the oxygen chamber. Nevertheless, we should feel greatly handicapped if we lacked facilities for supplying oxygen to patients with cyanosis.

SODIUM CHLORIDE

Another physiological alteration in patients with pneumonia is a decreased excretion of chlorides in the urine and a diminution of the chloride content of the blood plasma. From time to time during the past 25 years, papers have appeared dealing with the saline treatment of lobar pneumonia. Recently attention has been drawn to the fact that both in lobar pneumonia and in pyloric or high intestinal obstruction the chloride content of the serum is decreased. It has been found that the administration of large amounts of salt-containing fluid to patients with obstruction or to dogs in which the condition has been produced experimentally results in a marked decrease in the intoxication and prolongation of life, and this has been used as an argument in favor of administering sodium chloride to patients with pneumonia. It is doubtful, however, whether there is justification for drawing this analogy too closely. It has been shown that the loss of chlorides in obstruction is directly related to the vomiting of the high chloride-containing gastric contents. The loss may be enormous, and loss in water may be correspondingly great. Under these conditions it is not surprising that replacement of the salt and water may be very beneficial.

On the other hand, the diminution of chlorides in the blood in pneumonia is minimal compared with that occurring in obstruction. Moreover, in patients that have been given 15 to 30 gm of sodium chloride per day, there is little evidence that the chloride content of the blood has been increased to normal amounts. Certain writers are very enthusiastic about this form of therapy. Other good observers are more cautious, but still believe advantageous results are obtained. Influenced by these opinions, we have given certain of our patients moderate doses of sodium chloride daily and have thought that, in some instances, abdominal distention was thereby diminished, and some decrease of the symptoms of intoxication was observed. It will require much wider experience definitely to decide these questions. One of Sunderman's patients developed subcutaneous edema

when receiving 15 to 30 gm per day, and other observers have noted the occurrence of pulmonary edema. Large doses should, therefore, be avoided. Our patients have received not more than 10 to 12 gm, usually 5 to 8 gm, in addition to that in the diet daily. The salt is given in capsules. Frequently nausea and vomiting result. McCann recommends that in serious cases 10 to 15 per cent NaCl solution may be given intravenously. Thirst is frequently increased following the administration of sodium chloride, and therefore the administration of fluids is facilitated. In so far, at least, the method is useful. In all cases of pneumonia, the attempt should be made to administer at least 3,000 c c of fluid daily. If the patient will not or cannot take this amount, it may be given in the form of normal salt solution intravenously. Additional calories may also be given by adding glucose to the salt solution.

At the present time the administration of sodium chloride to pneumonia patients should be considered to be in an experimental stage, and the basis for this form of therapy largely empiric. One must always remember that modification of physiological alterations present in disease does not necessarily increase the patient's chances of recovery. Most of us remember when antipyretic drugs were in their heyday. Today, fever is being produced artificially in attempts to cure certain infectious diseases.

DIGITALIS

Much has been written about circulatory disturbances and about the failing heart in pneumonia. Contrary to the usual opinion, my own experience has led to the view that the early intoxication in pneumonia rarely manifests itself by injury to the heart, and that circulatory inefficiency is usually a late manifestation of the disease, occurring at a stage in which drugs can be of little value. Most patients die in pneumonia, not from cardiac failure, but from disturbances in respiration. Observation of the character of the breathing (frequently gasping and shallow, with laboring of the muscles of respiration) gives much better prognostic information than measuring the blood pressure. Of course, in the later stages of pneumonia, gradual lowering of diastolic pressure with loss of tone in the peripheral vessels and signs of cardiac dilatation do occur.

The question of the employment of digitalis in pneumonia is not yet entirely settled. In 1916, on account of the considerable number of pneumonia patients showing cardiac irregularities, and because of the known danger of attempting to digitalize the heart rapidly, the method of giving all pneumonia patients moderate doses of digitalis was introduced into our clinic. In 1930, however, Niles and Wyckoff reported that in a large series of cases treated with digitalis, the mortality was considerably higher than in a corresponding series of cases receiving no digitalis. In the light of this experience, Cohn and Lewis carefully reviewed all our cases. The conclusion reached was that giving digitalis did not seem to influence the course of the disease. As a result of these studies we have discontinued the

routine use of digitalis, employing it only under conditions, such as auricular fibrillation, where it would ordinarily be employed, even though no pneumonia were present, and then in exactly the same manner

In cases where there is a progressive fall of the blood pressure, it is our custom now to rely on intravenous infusions of normal salt solution with, if necessary, injections of ephedrine

It is needless to discuss here the other drugs that have been used in the past to stimulate the heart, frequently as a routine, before any signs of cardiac weakness have appeared—caffeine, strychnine, camphorated oil Today I think there are few advocates of this form of therapy

QUININE AND ALCOHOL

Besides these measures, intended to relieve certain symptoms and to overcome definite physiological alterations, numerous methods have been proposed which are supposed to have a definite action on the infectious process, the nature of the action, however, not being understood at present, or only explained by theoretical considerations Ever since pneumonia was first recognized, modes of treatment have appeared, flourished for a time, and then disappeared One has only to recall the vogue for blood-letting which flourished in waves from the time of Hippocrates, had an enormous vogue in the seventeenth century, and was still recommended and even somewhat widely employed in my own early medical days There were periods in which failure to bleed and actively purge with tartar emetic was ground for malpractice suits

Certain drugs, as alcohol and quinine, have been thought to have a specific action in this disease, and are still employed by certain physicians I have had little experience with the intensive use of quinine, but early in my medical life saw patients treated routinely with large doses of alcohol My recollections of this experience are not pleasant It is generally held that in alcoholic patients it is wise not to discontinue its use completely, and this seems sound and is the custom in our clinic

Other measures which have a vogue today and concerning the value of which the evidence is more or less conflicting, are diathermy and artificial pneumothorax

DIATHERMY

Several years ago, influenced by the reported favorable results from the use of diathermy, Binger and Christie in our clinic carried on studies with the idea of determining its value During the passage of the diathermy current they made direct measurements of the temperature which developed within the lungs in dogs, both in the lungs of normal dogs and in those which were the seat of a pneumonic consolidation It was found that in normal lungs in no instance was it possible to demonstrate any considerable amount of local heating, the explanation being that the lungs represent an excellent watercooled system, and that the intact pulmonary circulation

prevents any considerable degree of local heating. In consolidated lungs of dogs, probably because of the disturbed circulation, it was possible to increase the local heating slightly but not more than one or two degrees. In three pneumonia patients direct measurements of the lung temperature were made by the aid of thermocouples enclosed in an ordinary Luer needle, which was inserted directly into the consolidated lung. In none of these patients was there an appreciable rise in lung temperature during or after exposure to the diathermy current.

In the light of these studies no further clinical use has been made by us of this method of treatment. One hesitates to state categorically that this method has no value. We grow cautious with experience. One can only say that it is not based on experimental or clinical studies that appear to be sound. Even though it were possible to raise the temperature within the lung, it would not necessarily follow that the results would be beneficial.

ARTIFICIAL PNEUMOTHORAX

Although artificial pneumothorax as a therapeutic procedure was carried out in a few cases of pneumonia in 1919 to 1922, the method was not employed to any considerable extent until within the past two years. The chief justification for its employment is that offered by Friedman, who stated that by the collapse of the lung a state of immobility or rest is produced which diminishes the absorption of toxic products, and promotes healing. At the same time the inflamed pleural surfaces are separated, thereby pain is relieved, enabling the patient to breathe more deeply and also to obtain mental and physical rest.

Most of the clinical reports, so far, have concerned small numbers of cases, and usually only moderate amounts of air were injected. The most extensive and careful study has been that of Blake in 42 cases. He has drawn attention to the fact that to obtain immobility of the lung it is necessary to inject sufficient air to produce complete collapse. He studied his cases by roentgen-ray examinations and found that the amount of air necessary to produce complete collapse varied greatly in different patients, and could not be predicted, but usually varied from 1800 c c to 2400 c c. From a study of his cases it is difficult to judge whether or not the procedure had a favorable effect on the outcome. He rightly avoids drawing conclusions from the mortality rate in such a limited number of cases. However, 10 of the 42 patients died. There is, on the other hand, no evidence that the treatment was harmful. In only one of the cases treated before 72 hours after onset did spread to the opposite lung occur. He speaks of the excellent therapeutic results in the early cases without interfering adhesions, but only 10 of his cases belonged in this category and he concludes that "the use of this operation as a therapeutic measure in selected cases is worthy of further trial."

In our clinic at the Rockefeller Institute, a small number of cases has been treated by this method, and a clinical report on nine thoroughly studied

cases has been made by Abernethy, Horsfall, and MacLeod. Since this report, 13 further cases have been treated, making 22 in all.

Confirming Blake's observations, it was found that large amounts of air were necessary to produce collapse of the lung and immobilization. Pleural pain was relieved, but in many instances where large amounts of air were injected there developed dull, aching substernal pain that at times was as distressing as the sticky pleural pain had been. Moreover, in some of these cases, there occurred an increase in the dyspnea, tachypnea and cyanosis. While no permanent harmful results could be demonstrated, the procedure could not be shown to exert any favorable influence on the course of the disease. In the more recently treated patients, only small amounts of air, sufficient to separate the pleural surfaces, have been injected, and in most instances the relief of pain has been definite.

Although apparently so far no serious results have followed the production of pneumothorax in patients with pneumonia, the method is not without its dangers. In two of our cases apparently rupture of the lung occurred, with the development of very high intrapleural pressure and widespread subcutaneous emphysema. Both of these patients were subjects of chronic pulmonary emphysema and the operation should probably not be undertaken in such persons. In five of our nine cases treated by complete collapse, there developed an accumulation of fluid in the chest, but in only two was it sufficient in amount to require aspiration. While empyema has developed in a number of the reported cases, this has not occurred as frequently as might have been anticipated.

While carrying out this procedure in pneumonia is not a serious or difficult operation, it is not one to be lightly undertaken by anyone who has had no previous experience with the technic of artificial pneumothorax.

CONCLUSIONS

From this brief review it seems evident that the only form of specific therapy proved to be useful and available at present is serum treatment in Type I pneumonia. Etiologic diagnosis should be made as early as possible and treatment started without delay. Care should be taken to have good serum and it should be administered in large amounts and its use continued until recovery is evident. Certain measures, such as the administration of oxygen and of sodium chloride, may be useful in overcoming pathological variations in the body mechanism.

The value of artificial pneumothorax awaits further study. At present its usefulness seems to consist in the relief of pain rather than in any effect on the infectious process. Finally, it should be stated that, while the solution of the pneumonia problem has not been reached, some advance has been made in the past twenty-five years. Not the least important part of that advance has consisted in the increase of knowledge concerning the nature of the disease and of the natural mode of recovery. The accrued knowledge should lead to acceleration of progress in the development of methods of treatment and cure.

THE RÔLE OF THE PERSONALITY IN PSYCHOTHERAPEUTICS

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A psychoneurosis is an involuntary and automatic disorder of normal people, based on hypersensitiveness and the relative imbalance of instincts, causing inner conflict between instinctive forces and adult, intelligent strivings and ideals. Some outward maladaptation to life manifests itself by typical symptomatology in the vegetative, somatic, emotional or intellectual fields, thereby functioning as a compromise between the demands of the instinctive forces and the higher intellectual and ethical aims, and as a protective mechanism against whatever is painful and unacceptable emotionally and intellectually. The particular form of neurosis which develops is determined by the relative composition of individuality and environmental experience.

The importance of the situation in the origin and development of the psychoneuroses has been forcefully and accurately demonstrated. While it is a recognized fact that certain types of situations in life are common to the origin of all cases of nervous illness, they are recognized as the precipitating causes only. They constitute an extremely important factor in the development of the various types of maladaptation, however, and may give the key to an understanding of the nature of the case, be the determinants of the ultimate prognosis, and indicate the pattern of the therapeutic approach. We believe, however, that the fundamental causes of the psychoneuroses lie within the individual himself in the form of a specific hypersensitiveness to sensation or to emotion, or to both.

The treatment of the psychoneuroses consists of three major efforts, namely (1) to disclose to the patient the original causes of this hypersensitiveness, including those of a basic constitutional nature, (2) to assist him in the development of insight into the origin, nature and function of the maladaptive reactions, (3) to use this understanding of the fundamental qualities of his personality as the foundation upon which to erect a more efficient plan of living. We believe that the origins of the psychoneuroses lie in the phylogenetic and ontogenetic development of the structure of the personality, and therefore constitute the essential guide to the therapeutic approach in each case. Hence, we shall devote the remainder of this paper to a consideration of this aspect of psychotherapeutics.

At the outset we must presume the acceptance of the principle of psychological integration in contradistinction to the pedantic attitude of parallelism, which implies a theory that mind and body "accompany each other

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but are not causally related." For many centuries man looked upon himself in terms of biological fragmentation. Isolated manifestations of his personality occupied his attention for certain periods of time to the temporary exclusion of all others. Sherrington, in 1906, brought out his inspiring work on the integrative action of the nervous system and forever changed this attitude of incompleteness. Adolf Meyer accomplished an even more useful piece of work when he emphasized the pragmatic significance of this principle of integration in the higher mental functions and between the various physiological and psychological levels. This implication not only assumes a relationship of structure, but includes as well a unity of action even more closely organized than the structural systems themselves. There is an interdependence and synthesis of function and action that frequently transcends our knowledge of nervous system localization, and even in the presence of disease processes and disorders of function, we still witness the evidence of an organized whole. This often persists in spite of partial disintegration in certain parts of the organism, either structural or functional. In spite of the great individual differences among various people, we always find this fundamental principle of integration as the major factor in the total organization of the human personality. The ideal of mental health is based upon this unity of the personality. In any therapeutic effort, therefore, this ideal is the basis for the development of an understanding of disintegration, as well as integration, and until the former is investigated subjectively and understood by the patient, the subsequent steps of psychotherapeutic effort leading to integration cannot be comprehended, and their value is lost to the patient. Unless each of the antecedent steps in this synthesis is fully understood by the patient himself there will be a succession of corresponding faults in the later stages of his understanding, and in his ability to synthesize all of its factors. We believe, then, that a review of the biological and developmental factors of his personality constitutes the first and most fundamental parts of the plan of reeducation.

There have been many overlapping classifications and descriptions of personality attempted. No two psychologists would agree as to its basic structure, its exact definition or its fundamental characteristics or distinctions. Study and observation by many individuals have resulted in an encyclopedic accumulation of facts and theories relative to the personality and its reactions and expressions. Frequently the terms "personality," "individuality" and "character" are confused and used indiscriminately.

Jung's concept of introvert and extrovert personality is altogether too restricted, and does not appear to give consideration to immediate antecedents. Kretschmer's plan of pyknic and asthenic types, although based upon biological and constitutional fundamentals, involves a typing of personality rather than an explanation of structure. It implies a consideration of character. Character is not a fundamental part of personality, it is an expression of it. Freud, aside from his overaccentuation of sex and the rôle of the unconscious, came closer to what we believe to be the truth in his

"Id-Ego-Super-Ego" idea, but he apparently minimized the essentially organic or physical elements in personality. Adler, in his individual psychology, is altogether too stereotyped and teleological, and, like Jung, disregards immediate antecedent circumstances. There are many other theories, but in our opinion they are more or less impractical because they do not carry causal implications.

It is our belief that the most useful and accurate concept of the personality structure is that based upon the theory of the psychobiological development of the animal kingdom from its beginning to the present. We believe that each individual personality is made up of the end-results of development, the residuals of growth and experience, integrated into certain actual and potential constituents which express themselves in four predictable types of specific reaction. These reaction types, the reflex, the instinctive, the intelligent and the ideal, are based on four developmental neurological levels of the nervous system. These four levels of reaction represent four major developmental epochs of the entire animal kingdom from the amoeba to man, and therefore explain the purely biological foundation of the concept. They are repeated in the development of the individual from birth to maturity, and supply an adequate background for understanding both the mature and the immature aspects of personality. They explain the phenomena of personality disintegration and retardation, and give a foundation for comprehending the antecedents of individuality and character. These reactions include the physical, emotional, mental and moral dynamic forces of life, which vary in relative strength in each individual. They undergo many specific modifications through certain conditioning influences of life from childhood onwards, and thus give us a basis for comprehending individuality and furnish adequate explanation for the antecedents and motivations of all types of psychoneurotic maladaptation. When these reactions are considered in the light of individual hypersensitiveness, they explain the degree of the dynamic responses. This concept not only satisfies the biological point of view, but has proved satisfactory in the understanding of the origins and determinants of psychoneurotic maladaptation, and in addition furnishes a convincing foundation upon which to erect a successful system of psychotherapeutics. It stands the practical test of experience. This concept bears a certain superficial resemblance to Freud's more recently developed figure of "Id-Ego-Super-Ego," which, however, is more apparent than real. Any question of its priority is settled for all time by the relative dates of publication. It was published in 1912, while Freud issued his book in 1921.

The first of these developmental levels, the reflex, represents the lowest type of biological adaptation as implied in the functions of the primitive brain stem, a stage of biological growth when the neurological elements were relatively simple. It is a purely physical or somatic type of response and does not imply a "mental" reaction as commonly understood. This type of response implies all those primitive, non-affective responses which occur outside of awareness, and which, through the process of conditioning and

repetition, have become incorporated into automatic neurologically determined functions. In this evolutionary stage there had not yet appeared any of the so-called higher functions of feeling or thinking. At this level are found those phylogenous influences commonly included in Jung's concept of "the collective unconscious." This primitive structure in man is represented in general by the spinal cord and the medulla. It is at this level that the constitutionally determined element of sensitiveness first appears. An understanding of the elementary functions and expressions of this level of reaction upon the part of the patient is necessary, and the development of this understanding is one of the first steps in the therapeutic excursion.

The second type of reaction is due to the development of the next higher level of neurological structure, the diencephalon, which, in the words of Tilney and Riley, "gives rise to the thalamus, the hypothalamus, the epithalamus and the metathalamus." When this region in the brain developed, there arose a new type of reaction known as the "instinctive." These instinctive tendencies are the raw forces at the bottom of man's behavior, so to speak. They function from birth to death. Some of these forces have to do principally with the individual's survival, with his security as an individual. Others function as forces which insure the procreation of the race, others for the welfare of the race en masse. Each instinctive reaction is as it is because of the individual's inherent structure and the functional organization of that structure. Man is timid and pugnacious, socially inclined, hungry, sexually susceptible because he is built that way and organized that way—born to react that way. But each man is apparently born unequal so far as the relative strength of the instinctive tendencies is concerned. Some men are "naturally" more pugnacious than timid, some more dependent on their fellow man, some more self-assertive than others and so forth. Many of these relative differences are observable at birth or very soon after, in short, before environmental experience could reasonably be supposed to have modified the raw material to any great extent.

Instinctive reaction is not, however, a simple mechanical reflex even in its primordial raw form. It involves the whole creature, his whole biophysical organization, together with many complex reflexes and is accompanied by much activity that does not necessarily appear on the surface, as has been ably demonstrated by Cannon. For instance, if the instinctive tendency to self-protection is aroused, there is a quick mobilization of all the physiological forces appropriate to escape. Almost at once the animal, be he man or rabbit, finds himself in the best possible condition for flight. The muscles of locomotion have become tensed, the circulation carries to them blood freshly loaded by the endocrine glands with material for the most effective and efficient action. Respiration is doing its part to keep the blood stream thoroughly oxygenated. The gastrointestinal tract's activities are throttled down to a condition of relative paralysis. Other physiological changes have taken place, all functioning in the same direction, until the creature is in an ideal state for the instinctive action of escape to take place.

While all this is going on, it is of course inevitable that the creature must be conscious of at least a large part of these changes. He is no longer comfortable, in fact he is distinctly uncomfortable. He may be aware of his dry mouth, of his rapid heart beat, of his trembling, tense muscles, but even if he is not aware of these specific items, he is at least aware of the sum total of the changes that have occurred in his bodily sensations, so that he *feels* a painfulness and at the same time as part of that uncomfortable feeling, a strong desire to escape, to discharge that mobilized energy and to rid himself of the discomfort as fast as possible. In short, when the instinct of escape is aroused, the creature is not only mobilized for escape, but *feels* that mobilization as a strong emotion accompanied by an intense desire to flee.

Thus an instinctive reaction may be said to have three parts just as the simple reflexes have three parts—the sensory, the central adaptor and the expressor or motor part. Each instinct can also be said to be accompanied by its own appropriate emotion which is either painful to some degree or pleasant to some degree, and which besides its pleasure or pain element has a second strong motivating force within it, namely, the desire to escape from or approach the object which has aroused it.

The instinctive make-up of an individual is the second structural element of his personality and individuality. Therefore, to understand him it is necessary to gauge as nearly as possible what the relative strength of instinctive forces in his inherent makeup may be. Is he more pugnacious than timid? Has he a relatively strong or weak social drive? Is he more self-assertive or more retiring than self-important? Has he a relatively strong or weak sex drive? Is he more or less suggestible than the average? By suggestible is meant the degree to which he is liable to the uncritical acceptance of ideas. It is an instinct-like quality present to some degree in everyone, usually greater in youth than in adult life, and varying in regard to any subject in inverse ratio to the amount of the individual's knowledge of that subject.

The development of insight upon the part of the patient into the nature of these instinctive reactions, especially those that have contributed largely to the origin of his own conflicts, is the second logical step in the development of the therapeutic teaching.

The third type of biologically determined reaction is the intelligent. It came about as the result of the further development of the telencephalon or end brain. Growth in this part of the central nervous system brought new capacities and abilities, a new function and a new type of reaction to the various stimuli of life. Just what intelligence is we do not know. The word is used very widely and as loosely as most psychological terms. Let us limit the meaning for our present use to its functional significance rather than to attempt a definition. Let intelligence mean the ability to understand, to comprehend whatever our senses bring to us and to judge of its significance. Let us add to understanding and judgment one other related sub-

function, namely, choice, which is the executive function of intelligence, and then the description will be sufficient for our present purpose

Obviously individuals vary widely in regard to the quality of intelligence they possess. Here again men are born unequal, some extremely well endowed, some with only an average endowment, and others poverty-stricken from birth. From the quantitative point of view alone then, intelligence is one of the fundamental variants determining the individuality. This characteristic varies greatly within the normal, but more in quality than in quantity. It would seem, in short, that people differ from each other even more markedly in the specific type of intelligence they have than in just how much of that master function they possess. One need only mention the vast differences among children, the mechanically minded, those who take to mathematics with marked ease, while others are "born linguists," to appreciate how important a variant within the normal this qualitative specificity of intelligence is in the equation of individuality.

These variations in the fundamental and functional, the inherent and acquired intelligence are of at least as great import to the understanding of any individual as the variations of instinctive make-up, for by virtue of the former his mode of adaptation to his world will be very largely determined.

In the ability to understand, to judge of the significance of things and to exercise choice, is observed the great adaptive control of all the foregoing primordial forces. It is that which enables us to understand our environment, our relation thereto, and last but not least, to choose among all the possible plans of action the one most likely to give us the results we desire. It is this faculty par excellence which constitutes man's ability to make his adaptation purposive, and this raises it from animal reaction to human behavior.

Finally there comes the fourth or highest level of the adaptive machine as represented neurologically by the growth and development of the neopallium. This level is known as the ethical and it is here that the most difficult integration takes place. Man's demand for the specific form of satisfaction and happiness which ethical conduct engenders seems to be a genuine biological development. Is it not indeed this very demand in each individual which makes civilization a biological necessity? In early time the instinct of self-protection underwent modification when man began to live in groups and the safety of the group had to take precedence over the survival of the individual as each man's objective, and thus simple society became a sort of mutual protective association where each individual was classified according to his material value to the group. A sense of individual responsibility toward every other member developed, probably the expression of a strong instinctive force released by the absence of the necessity for self-protection, which grew as part of the progress of society toward civilization. This desire to protect, this responsibility for the welfare of the other fellow no doubt spread from its earlier exclusive application to

members of the individual's own group, until it included those of other groups and finally, as an ethical idea, became all-embracing

However, the ability of the individual human being to function ethically is apparently acquired through training, example, education and other forms of experience, for although there is an inherent drive in this direction, the acquirement of it takes many years, beginning in infancy and continuing into old age, at least to a diminishing degree. It is upon this level that the unified energies of man come to fruition in the form of purposive striving and it is here that man erects his philosophy of life

An item which affects individuality very definitely and which varies greatly even within the normal is mood. Let it be understood that by mood is meant the general tidal level of affective activities, the height or depth of the feeling level. The top of the tide represents the mood of exaltation and a full moon flood tide, transcending the normal, will represent manic elation. The ebb tide, on the other hand, pictures gloominess, blues, and the extreme ebb, beyond the normal, would represent the depressed phase, the melancholia of a manic depressive episode. But well within the normal there are mood swings both up and down sufficiently marked to affect not only feeling but thought and action as well. Normal people vary from each other in the degree to which they are subject to mood swings and also as to whether these swings are habitually up or habitually down, and as such mood swings tend invariably to affect both thinking and acting, they can neither be ignored in understanding an individuality nor neglected when dealing with a person's difficulties in adaptation.

There is one all-qualifying item in the equation of individuality which, according to our present formulations, comes neither under intelligence nor instinct, but, nevertheless, has to do with both and with every other characteristic of every human being, and that is temperament. This word has been used so freely and so carelessly not only in common parlance by the man in the street, but also in psychological literature that it may connote anything from the sum total of human characteristics "to an overworked alibi for being dirty, careless and never paying one's bills." So here again we must limit the meaning of the term to something definitive and practical. In this case let temperament equal sensitivity and, to be more specific, let it equal that particular degree of sensitiveness to the painful or pleasurable in sensation and emotion, thought or mood possessed by an individual. Even shortly after birth it can be observed how infants vary in acuity and completeness of reaction to stimuli both internal and external. Even babies manifest a degree of sensitiveness so that "he who runs may read." It is almost equally obvious in adults in spite of the modifying influence of experience and training, for in them that sensitiveness to the pain-pleasure element in experience has already become highly specialized, highly specific. In short, through experience this sensitiveness becomes specific to the instinct or instincts which are inherently relatively overactive or which have become so through experience. Therefore, the finished product will manifest his

sensitiveness in particular and often easily observable directions. This sensitiveness is a very real thing physiologically as well as mentally. For instance, a hypersensitive person who is at the same time more timid than pugnacious not only needs more courage to achieve even ordinary aims, but will show his sensitiveness to fear not only in the necessity of more than ordinary courage but in the aggravations of the physiological reactions characteristic of fear. These may manifest themselves in disturbances of the gastrointestinal tract or of the heart's action, by sweating or by blushing and blanching, or in short, by undue disturbance of any or all of the functions under the dominion of the sympathetic system.

Obviously the effect of variation in this characteristic upon the individuality as well as upon the technic of the person's adaptation may well be striking. The part that it plays in normal life, its functions as an asset, as well as its rôle in psychoneurotic maladaptation, its liability aspect, is one of the main concerns of psychotherapeutic treatment.

To recapitulate briefly, the component parts of personality and their respective neurological levels are

First, the level of vital reflex under the dominion of the medulla.

Second, the primal inherent forces called instinctive in which we follow very roughly McDougall's classification—instincts which serve self and those which serve race and species, represented on the neurological level by the thalamic region of the brain.

Third, intelligence, that characteristic which modifies or adapts the primal forces to a wider, more elastic and diversified use, represented neurologically by the fore-brain.

Fourth, the super-intelligent or ethical level, represented by the latest and most complex development of the fore-brain, particularly by the frontal lobes.

Finally, to complete the picture of individuality, we must include mood, temperamental-sensitivity, items which directly qualify the primal forces, as well as intelligence, by affecting the quality and intensity of their action.

These are the variables in the human equation which in their reaction to one another and through their organization as a whole constitute the bio-psychological entity, the individual, who in ways that are characteristic of the race, on the one hand, and of himself individually on the other, reacts to his environment and to which the environment reacts.

These four levels of biological development, which represent the evolution of the adaptive processes of the animal kingdom, are repeated in the growth of each individual. They must be studied in regular order and thoroughly understood by the patient before he can comprehend the various factors that have preceded his maladaptations.

At birth this machine is imperfectly developed and immature, and, therefore, functions only in part. The process of maturation is determined and affected largely by the nature and character of the environmental influences, i.e. the stresses and disciplines which surround the growing child. On his

way toward maturity, the individual may undergo certain experiences, real or imagined, which tend to condition or modify him to fix his reactions at definite chronological levels and often relegate many of them to the unaware regions of consciousness. It is by this process that the useful experiences of the individual become stored away and made automatic, thus relieving the intelligence of the necessity for repeatedly thinking out solutions for the many new situations that arise in his daily life. It also frees the intelligence and makes it available for use in new experiences and for making adjustments on the purposive plane, but it is also during this process that immature emotional values may be given, more or less permanently, to reactions, which reappear in adult life as though they represented present experiences. Frequently these experiences represent conflicts between the various reaction-levels of the personality and furnish the basis for the origins of the psychoneuroses. Recent environmental situations may reactivate those old emotional values through association and thus contribute to the causes of the maladaptive reactions. Thus it becomes necessary that the individual should possess insight into these motivations and the development of this insight is an important factor in an effective therapeutic effort.

At birth the normal infant is equipped with a potential capacity for the development of all four of these levels of adaptation. Actually he is largely a mass of reflex reactions, many associational tracts are not yet myelinated and he remains in this condition for a relatively long period after his birth. He is the most dependent creature on earth. He cannot express his needs or his desires in the language of his environment. He cannot move toward the sources of his food supply. He would die of starvation and exposure were it not for the assistance given him in this first stage of his development. He is non-logical because intelligence has not yet developed. He is non-moral, having no group consciousness, and he is completely egocentric and as yet has no concept of "I" or "You". The security of food and protection from the elements are his only needs and are supplied by those around him. Later his psychological needs are furnished by the attention, love and approval of the individuals who constitute the parental group. Because of his immaturity and inability to comply with the laws and customs of this group, the child lives in a world of criticism, admonition and discipline. The first words usually spoken to an infant after the excitement of his arrival has passed is the negative "No! No! Mustn't do that!" Later, these attitudes of constant correction upon the part of the adults (one author calls them "Giants") are frequently unconsciously interpreted as a withdrawal of parental love, or as a possible threat to this love, unless they are balanced by the opposite attitudes. Because of his nature the child cannot mature uniformly and completely without this affection as expressed in approval. He therefore attempts to modify his own demands and conduct, so as to comply with the arbitrary demands of the environment in order to obtain it, in spite of his own wish to act in the opposite manner. He senses, sooner or later, that cooperation with these

external demands brings him the pleasure which the attitude of approval upon the part of the parent excites within him. Parental attitudes, then, become the first and most important factor in conditioning the child's early psychological existence.

As time goes on and the child grows older the instincts become more and more prominent and determine in an increasing degree the motivations of his conduct. As the instinctive desires, needs and demands for gratification become stronger, the greater becomes the conflict between the child and his environment, and the more difficult becomes the solution of the problem of the socializing of his instinctive forces. Eventually the child begins to comprehend the meaning of the contrary attitudes of the parents, but because of the power of the non-logical and non-moral instincts he is bound to have a certain degree of difficulty in complying with them. We tend to forget that he is not just a small adult and expect altogether too much of him. He is but an immature child and he does not yet possess the adaptive machine of an adult. The result of unwise parental attitudes is repression. The more severe the parental authority and the more sensitive the child, the more numerous and deeper become the repressions, or the more violent are the rebellion and resentment against parental authority. The more exaggerated and persistent the authority, the more the repressions become charged with overdetermined emotional values.

Because of the rapidity with which each new experience comes to the child, and the necessity for learning quickly the difficult business of adaptation, there are many experiences which are thrust into the realm of unawareness in an unfinished condition and partly or wholly forgotten, although the emotional force attached to them may remain active. The child mind cannot make accurate interpretations or determine correct values in many of these new experiences, and consequently these are stored up in his mind with fictitious values attached to them. These overdetermined and little understood emotional experiences may lie in the unaware region of his consciousness for years in an unfinished and unresolved state and may thus continue to furnish the motives for thoughts and conduct which are frequently inexplicable to outsiders as well as to the individual himself.

There comes a time in the stages of development when an entirely new element makes its appearance in the growth of the personality. Its arrival is not as abrupt as this statement might imply for it makes its appearance gradually and, at first, in minor, simple manifestations. It is the development of the ego or selfhood and occurs at the level of intelligence and at about the same time as the aggressive instincts become more prominent. Self and the awareness of self undergo accentuation, but he also becomes aware of himself not only in terms of the drive of self-importance and self-expression but also as an individual striving for the ethical objectives in his relationship with others. He begins to identify himself with his own kind and tries to act in the manner of an independent adult.

Soon the world of the child enlarges, and he finds himself more or less

on his own in contact with people both young and old outside of his own immediate family group. The child is at first confused by the apparent disagreement between his formerly unquestioned parental authority and the actual facts of life as he now observes them. Here before his eyes is another child doing the very things prohibited by his own parents, and escaping the punishment which he had learned to expect. What does he do? He begins, with much trepidation, to use his newly acquired ego and its correlative intelligence. He begins to experiment. He begins to use his new aggression. To his amazement he discovers that he also escapes the consequences predicted by his parents. Thus he goes through a period of disillusionment and reevaluation. He discovers that certain laws set up by the parents are not universally accepted and that certain parental attitudes and opinions are not necessarily correct. He discovers that in fact they are frequently met with ridicule, disrespect and complete rejection by his fellows. As the result of these experiences, he modifies the ideals set before him by his parents and builds up ideals and principles of his own. As he slowly becomes wiser through experience, he builds his own authority and forms his own opinions. He gradually learns to renounce the gratification of obedience to parental authority, and becomes less and less dependent upon it for his inner comfort and satisfaction. But regardless of how old he becomes and the degree of wisdom to which he attains or the extent of his sophistication he never becomes completely mature emotionally. There is no such object in nature as an adult who is completely mature emotionally. The effects of many forgotten admonitions and criticisms in childhood, of prohibited acts, phantasies and thoughts of the immature period may still be present in the unaware consciousness of the adult, influencing thought and conduct and consequently affecting the habit patterns of character. These conditioning influences of childhood are perhaps the only important environmental factors, for the specific way in which the individual reacts to them is due primarily to his particular constitutional make-up, whether he meets criticism and discipline with open and successful rebellion or retires to his corner whipped and assumes the rôle of the overgood child or becomes a nervous, irritable, frightened person depends first upon the degree of sensitiveness with which he was born and his inherent instinctive make-up, and only lastly upon the stimuli arising from the environment.

Therefore the physician cannot be content in unearthing ancient conflicts between conscience and instinct but must discover and help his patient to understand what inherent qualities of his own personality caused him to react to these common difficulties in such a way as to contribute to the formation of a psychoneurosis.

We have said that the treatment of the psychoneuroses consists of three major efforts.

- 1 To disclose to the patient the original causes of his hypersensitiveness, including those of a basic constitutional nature, if possible.

2 To assist him in the development of insight into the origins, the nature and the function of the maladaptive reactions

3 To use this understanding of the fundamental qualities of his personality as the foundation upon which to erect a more efficient plan of living in the future

Studying the patient according to the method suggested in this paper, and with the knowledge gained from physical examinations, laboratory studies and careful survey of the patient's heredity, etc., we are frequently able to find and disclose to the patient his inherent hypersensitiveness and the specific nature that it has acquired. This fulfills item one of the psychotherapeutic program.

In taking the patient through his own growing-up processes by helping him to give the fullest possible history including an account of parental, social, educational, religious and other influences, supplemented if need be by controlled association, we endeavor to find the sources of his difficulties in adaptation, including such overloaded emotional values as may be associated therewith. This should result in the gradual development of insight into the origins of his troubles. As he gains perception he becomes aware of the real nature of his illness, and finally is able to realize that his nervous condition is functioning as a means of defense or escape. Ultimately he becomes aware of the fact that his illness is the result of his own hypersensitive reactions to the circumstances of the environment rather than that the environmental situations are more powerful than his personality and his ability to handle and solve them. This completes the second state of reeducation.

Finally, the third effort in the reeducational process is begun. In this stage the patient uses the knowledge he has gained of the elements which constitute his personality. He has already developed an intimate knowledge of those elements of his personality which have been responsible for causing his neurosis. With the help of the patient and by thinking *with* him in place of thinking *for* him more practical concepts of life are built up and better planes for a balanced life can be formulated.

When the period of intensive reeducation has been completed and there has been some incidental but important practice in the daily application of the principles taught, the patient is discharged and returned to his own environment for a trial trip. Following his discharge, close contact is maintained in order that his progress may be supervised, which is accomplished by one or more return visits of brief duration for review and advice.

TOTAL LEUKOCYTE COUNTS IN HUMAN BLOOD DURING PREGNANCY ¹

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VIRCHOW spoke of a physiologic leukocytosis of pregnancy and by the weight of his authority the assumption was given validity, repeated in textbooks, but as far as can be found out, never very seriously investigated. De Lee ¹ elaborates the idea by stating that during pregnancy, from the first few months, there is a decrease of the red blood cells and an increase of the white blood cells, the latter out of proportion to the former yet seldom exceeding 15,000, that the younger forms increase so that the blood of pregnancy resembles that in an acute infectious disease, and further that the changes are more marked in primiparae. Williams ² mentions a leukocytosis during labor. Cragin ³ gives some average counts during pregnancy 10,600, during labor 12,800, the third and tenth days post partum 11,700 and 10,300. Polak ⁴ says that extreme changes are not seen, but that the number of white cells is increased and especially so in the later weeks of pregnancy. Jellett and Madill ⁵ repeat what appears in other texts, namely, that there is an increase in the white blood count toward the end of pregnancy. Bland ⁶ is a little more specific in that he sets an upper limit at 20,000, and declares that there is invariably an increase. Both of these latter authorities mention that the increase is largely polymorphonuclear and more likely to be marked in primiparae. Piney and Wyard ⁷ and Piney ⁸ specify a neutrophilic shift to the left, usually without any evidence of infection, and particularly definite in the later months. They assume it to be a physiologic condition. Inasmuch as there have seldom been actual figures given to substantiate these often repeated statements, we determined to establish, if possible, a basis for proof or disproof.

We have gathered together 977 white blood counts from 134 presumably normal pregnancies, 169 pregnancies were studied, but only those cases in which five or more counts were obtained were finally tabulated. Practically all of these women had, either during the period of prenatal observation, post partum, or at some other time contiguous to the pregnancy, a physical examination. They were all considered to be normal women. There were no abnormal conditions during the prenatal period of observation that we thought could in any way affect the leukocytic level. The only infections found were upper respiratory infections in four, Trichomonal vaginitis in four, acute enteritis in one, cervicitis in three, pyelitis in three. Only in the latter might there have been some effect on the white blood

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TABLE I

Leukocyte Counts in Pregnancies during Which Pyelitis Occurred

Mo	Primip 1		Primip 2		Primip 3	
	W B C	Urine	W B C	Urine	W B C	Urine
II	12,550	pus				
III	15,000	"	9,500	clear		
IV	9,900	clear				
V	13,550	pus	12,050	pus	11,300	clear
VI	14,100	"	12,300	"	14,000	"
					14,850	"
VII	10,100	"			11,850	pus
VIII	10,400	"	12,600	"	12,750	"
					10,100	"
IX	8,900	"	11,950	"	12,000	clear
	9,250	"	11,950	"	10,350	
	10,650	"	8,200	"	12,450	

count (table 1) It will be seen by comparison with the other tables that the increases in these cases are not greater than those often seen in women entirely free of infection (table 2, case 2, for instance)

There were 92 primiparae There did not seem to be any consistent difference between the level of blood count in these cases compared with that found in multiparae (table 2) A few instances in which the same

TABLE II

Leukocyte Counts in Pregnancy, Comparing Primiparae, Multiparae and Non-Pregnant

Mo	Primip 1	Multip 2	Primip 3	Primip 4	Multip 5	Primip 6	Primip 7	Primip 8	Multip 9
	Other W B C not pregnant		6,800	18,150† 15,050	8,600	6,550† 5,650	6,700	10,000	
II			7,750		16,050	9,050		13,450	7,450
III	7,600	10,850	6,350	14,500		8,150		10,000	
IV	10,250	13,200			10,750	8,250		8,500	10,950
V	10,350		9,350	19,400	10,000		7,800	10,450	Intermittent Bleeding
								10,250	
VI	7,050	15,650	7,850	17,600		11,850		9,200	
VII	7,950	12,750	8,450	20,650	12,750	12,100	6,150	10,250	
		13,800		18,500				9,000	
VIII	8,650	12,800	6,250	16,100	11,800	12,150	7,700	11,750	
	7,650	13,800	8,600		11,150			9,100	
	9,000								
IX	10,150	19,400	9,950	15,800	8,150	9,950	7,300	10,000	7,950
	8,500	15,750	8,650	17,950			6,800		10,800
	8,350	15,000	8,900	18,450			7,800		8,450
	8,050	16,250	8,250						
			7,450						
			7,750						
			8,300*						

* Two days before delivery

† Acute upper respiratory infection

‡ One year later—in hospital for gall-bladder operation

TABLE III
Leukocyte Counts in More Than One Pregnancy in the Same Patients

Mo	Case 1		Case 2		Case 3		Case 4	
	1st Preg	2nd Preg	2nd Preg	3rd Preg	1st Preg	2nd Preg	1st Preg	2nd Preg
II				12,350				
III	10,150					9,200		
IV	11,650	10,400		7,100	6,550		8,900	9,750
V	6,900	13,100	7,800			5,900	7,650	7,900
VI	7,900	8,850		9,400	6,250			10,150
VII	9,850	10,250		8,500	5,750	8,050	9,900	
				8,000			9,900	
VIII	9,400	8,750		9,900		5,900		8,050
		8,100		10,150				8,500
IX	8,950	13,050	10,350	8,150	5,900	8,150		6,450
	7,250		6,800	8,600		8,550		
	8,200		6,700	8,300				
			6 yrs ago not preg 7,900					
			4 yrs ago not preg 7,800					

woman was observed through two pregnancies, are tabulated (table 3). In a few isolated cases we found in the record white blood counts done when the patient was not pregnant. In some these differed, in others the pregnancy count corresponded very well with the interval count (tables 2 and 3).

All of these counts were done by one technician (H. B.), and most of

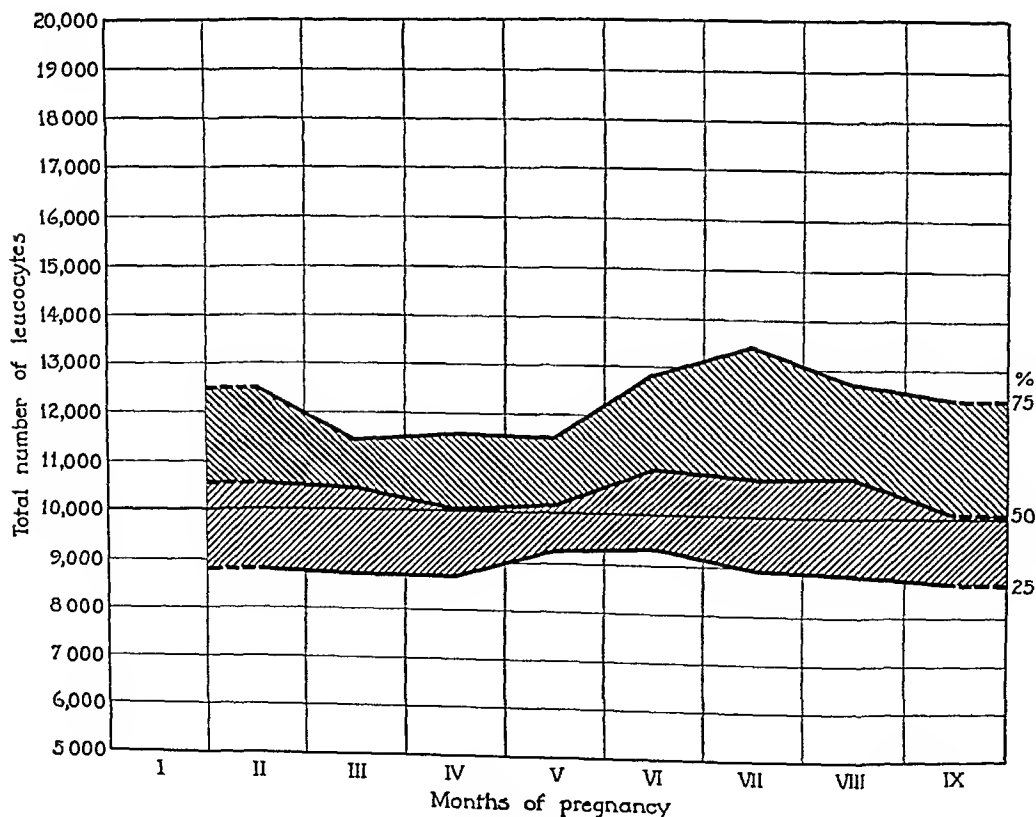


CHART 1

them were taken in the afternoon, usually later than two hours after the noon meal. A few counts were taken in the morning, usually about three or four hours after a meal. No attempt was made to control any factor which might affect the count, such as exercise, anemia, etc. All of the patients were ambulatory office patients.

We have chosen to chart the median curve, since the counts are not evenly distributed throughout the whole period of gestation, nor for any given month, and such a curve more clearly indicates the center value. The median is the middle case, so that 50 per cent of all counts are above and 50 per cent below. We have also charted the percentile lines, establishing the four quartile zones of variation. Lacking values of normal for non-pregnant women, we have assumed 10,000 to be the probable upper limit of normal, since counts higher than this are commonly considered pathological by most clinicians (chart 1).

There were in general three types of curves seen in a study of individual cases: one a curve that approximated the median one charted (table 2, cases 1, 5, and 6), another which remained throughout on a high level (table 2, cases 2, 4, and 8), and a third which remained throughout on a level well within normal limits (table 2, cases 3 and 7). It is apparent from the charted curves of median and percentile values, and also in the individual cases cited, that there is no consistent rise in the ninth month, also that less than 50 per cent of the counts are below 10,000. The impression is that some women respond with a leukocytosis to pregnancy and others do not.

There was nothing unusual in the cell morphology of those cases showing an elevation of the white count. The elevation seemed to be predominantly of the neutrophilic cells.

SUMMARY

1. Nine hundred and seventy-seven leukocyte counts in 134 normal pregnancies were obtained.

2. A count between 10,000 and 11,000 seems to be a median value for pregnancy, irrespective of time in pregnancy.

3. Fifty per cent of the counts were between approximately 8,700 and 12,500 throughout the nine months of pregnancy.

4. Less than 50 per cent of the counts were below a high normal of 10,000.

5. Seventy-five per cent of the counts were above 8,700.

6. Twenty-five per cent of the counts were above 12,500 or below 8,700.

7. There was no rise in the ninth month, except in a few individual cases which were not numerous enough to lift the curve.

8. Some patients remained consistently high throughout the nine months, others remained consistently low or normal.

9. There did not seem to be any significant difference between curves of counts in primiparae and multiparae.

10 There may be a physiologic leukocytosis of pregnancy, but it certainly is not invariable

We are indebted to Dr Edith Boyd for her help in preparing chart 1

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THE CONTINUOUS METHOD OF TREATMENT OF EARLY SYPHILIS ¹

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If early syphilis is properly treated, late syphilis will almost, even if not quite, disappear. That early syphilis is not being properly treated is obvious from the fact that late syphilis is not disappearing. On the contrary, in every urban American community syphilis heads the list of reportable communicable diseases, and of the cases reported, more than half are late cases ¹

The proper treatment of early syphilis is of importance from three standpoints: that of the individual patient, that of the public health, and that of the public expense. The individual patient requires proper treatment in order to accomplish "cure" and to prevent the development of usually serious, often crippling and disabling, and sometimes fatal late lesions. To utilize the two most serious of these, cardiovascular and neurosyphilis, as an

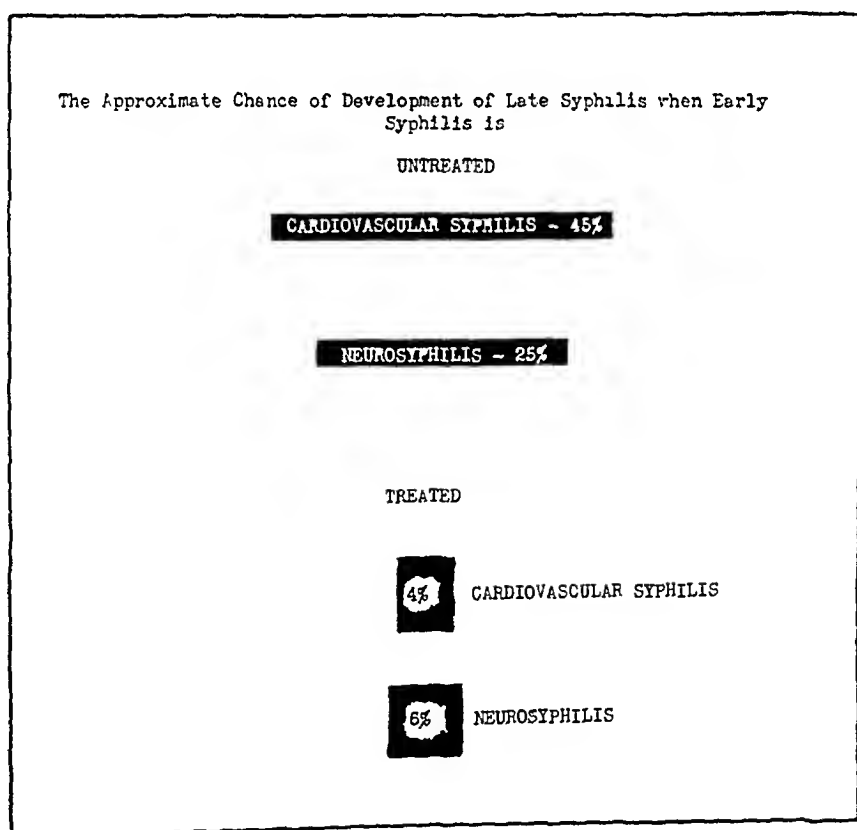


FIG 1

* Presented at the Detroit meeting of the American College of Physicians, March 3, 1936
From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital

illustration figure 1 shows the approximate incidence of each in patients untreated or badly treated as compared with those given adequate early treatment. Similar data are available for all the late sequelae of the infection.²

From the standpoint of the public health, the spread of syphilitic infection may best be controlled by the elimination of the infectious patient

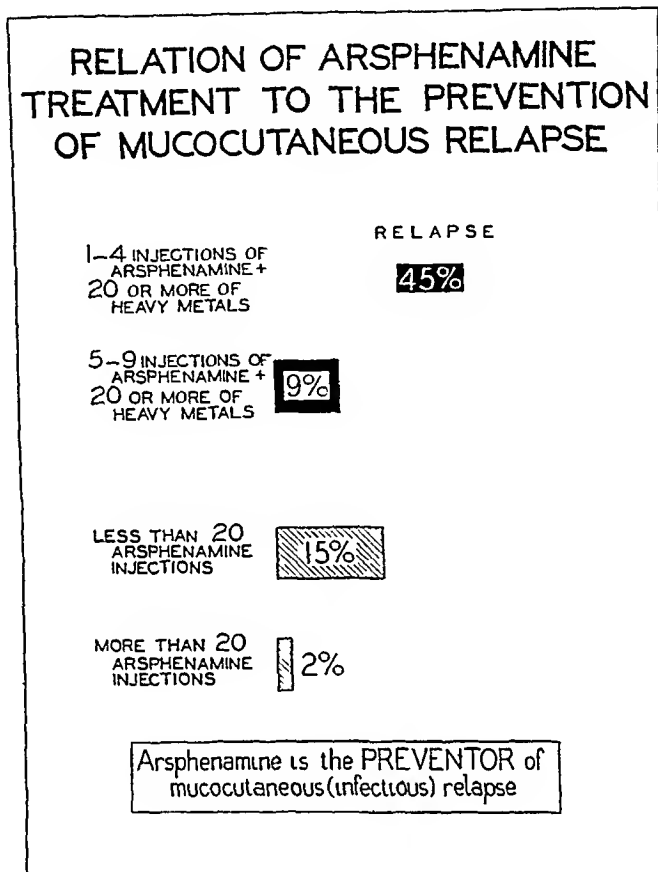


FIG 2

Figure 2 * shows that (1) an arsphenamine is necessary to prevent infectious relapse—heavy metal alone does not suffice, (2) less than four injections of an arsphenamine permits relapse in the astonishingly high total of 45 per cent, an incidence probably even higher than would occur if no treatment were given (though data on this form of relapse in untreated syphilis are lacking), (3) at least 20 injections of an arsphenamine are the absolute

* All figures except figures 1 and 10 are based on the data of the Cooperative Clinical Group (the Syphilis Clinics of the Universities of Pennsylvania, Michigan, Western Reserve, Johns Hopkins University, and the Mayo Clinic). The papers on which these charts are based are listed in the bibliography as reference 3.

Figures 2, 7, 8, and 9 have been prepared by the American Social Hygiene Association and are here published for the first time with permission. These and 19 other similar figures illustrating the studies of the Cooperative Clinical Group on early and latent syphilis are available in pamphlet form (price 30 cents) from the American Social Hygiene Association, 50 West 50th Street, New York.

minimum required nearly to eliminate infectious relapse. The practical abolition of infectious relapse is related not only to the total amount of treatment given, but also, as will be shown, to its type. It is important here to emphasize, however, that the public health aim of treatment, and the end sought in the individual patient, require a type and total amount of treatment not very different for the one than for the other.

The economic aspect of the proper treatment of early syphilis is of fundamental importance. Hospital beds, both general and psychiatric, are filled with patients who must be treated and maintained at public expense, who are no longer a menace to the public health since they are no longer infectious, and whose prospect of "cure" or even of symptomatic relief is, as compared with early syphilis, negligible. In Baltimore, the annual expense of hospital care for such patients, for the average year (determined in 1933) is \$100,000.⁴ If this sum is expended in one city of not quite a million people, it is a fair estimate that the hospitalization of broken down late syphilitics (whose illness is nearly irremediable) in the country at large costs approximately \$12,400,000 annually. The amount of money expended by Health Departments and privately endowed hospitals on the ambulatory care of patients with early syphilis, i.e., at a time when "cure" can be accomplished and the development of late sequelae requiring hospitalization prevented, cannot be so readily estimated but is probably nowhere nearly so large a sum. It seems logical to conclude that the expenditure of money is being made in the wrong place, and that by increasing greatly the amount spent on the proper care of early syphilis, the ultimate cost of late syphilis could be greatly reduced.

If one grants that, by and large, early syphilis is not being properly treated, it is wise to enquire into the reasons for this difficulty. The fault seems to lie in part with the biology of syphilitic infection, in part with the laity, and in part with physicians.

It is now quite clear that in some patients, perhaps in many, who are infected with syphilis, the lesions of primary and secondary syphilis are either wholly absent or so trivial and transitory as not to attract the attention of even the most observant individual. Infection has been, for all practical purposes, symptomless. If a patient does not recognize symptoms serious enough to take him to the physician at all, obviously he cannot be treated. Such patients form an as yet unmeasured reservoir for the spread of infection to others, and for the ultimate development of late syphilis. The physician has only one defense against this biologic silence of syphilitic infection, namely the use of the routine serologic test for syphilis on every possible occasion. Case finding is as important in syphilis as it is in tuberculosis.

The fault which lies with the laity is ignorance, and worse still, unwillingness to learn. Many individuals, perhaps most, know little or nothing of syphilis—its symptoms, its late complications, its prevalence. Most persons know only that the disease is "venereal" and usually contracted through sexual intercourse. The sex taboo forms the barrier to the acqui-

sition of accurate knowledge. There is a "conspiracy of silence" concerning syphilis. The press, daily and periodical, and the radio, too often bar even the mere mention of the word, let alone informative discussion concerning it. The public must be educated to know what syphilis is, and trained to consult a physician for its earliest symptoms as it has been similarly trained for tuberculosis and cancer. The dangers of quack, drug store, or self treatment must be pointed out. Until the patient knows enough about his possible illness to consult a physician for it, the hope of getting him under early treatment is an idle one. Until he knows something of the requirements of proper treatment, and the possible consequences of evading it, it is useless to expect his cooperation in carrying it out.

The fault of the medical profession is threefold: that it has not taken the lead in education of the laity, that it does not apply modern methods to early diagnosis, and that, though adequate treatment methods have been developed, it does not apply them. Further discussion of the educational aspects of the problem are beyond the scope of this paper. It is essential to point out, however, that the reasons for the failure to control the syphilis problem are not wholly due to the inadequacy of current modern treatment.

To concentrate now on the question of treatment, it is readily apparent that the failure of physicians as a group is due in small part to technical ineptitude, and in large part to the persistence of empiricism. There are a few simple principles applicable to the treatment of early syphilis, all of which are backed by sound experimental and clinical evidence. These are

- (1) Successful treatment depends on early diagnosis
- (2) The choice of drugs is limited to the arsenicals represented in the arsphenamine group, and to bismuth
- (3) Treatment should be continuous from start to finish, i.e., without rest periods of any sort
- (4) Treatment must be prolonged to a minimum of (depending on the stage of infection) 12 to 18 months
- (5) Determination of "cure" requires life long post-treatment observation

The importance of early diagnosis is shown in figure 3. The patients on whom this chart is based were treated by several different methods and in varying amounts—not with the best method and for the optimum time. Even with this handicap seronegative primary syphilis is 72 per cent "curable", whereas the prospect of "cure" drops by 20 per cent with the few days' or weeks' delay necessary for the development of a positive serologic test or secondary lesions. To increase the probability of early diagnosis of seronegative primary syphilis, it is essential (1) to educate the layman to consult a competent physician at once on the appearance of any genital sore, (2) to educate the physician to use the dark field microscope or to refer his patient to some one who can.

The choice of drugs is limited to the arsenicals represented in the arsphen-

amine series, and to bismuth. This point should not require elaboration. No other arsenical drug is known which is of comparable value to the arsphenamines in early syphilis, though one still sees patients treated with

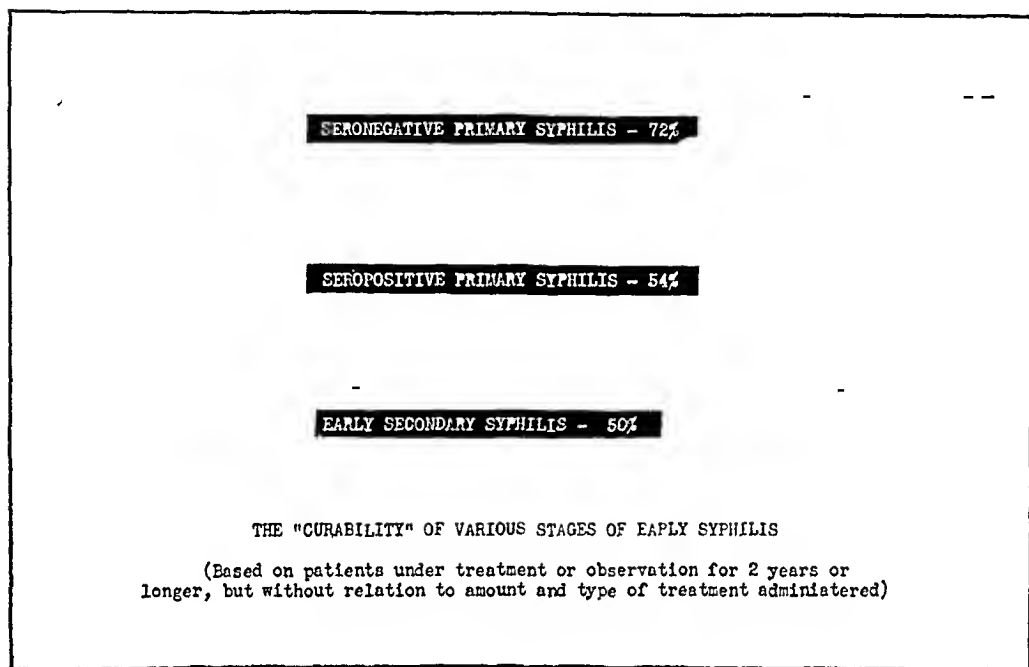


FIG 3

pentavalent arsenicals (useful only in neurosyphilis), with sodium cacodylate, or with bizarre and untried arsenicals boosted by pharmaceutical houses. Among the arsphenamines, only arsphenamine itself (606), neoarsphenamine (914), silver arsphenamine, and mapharsen (arsenoxide) are worthy of serious mention, and in spite of the 25 years of study devoted to the subject, a serious comparison as to the relative merits of these four is available only for arsphenamine and neoarsphenamine (mapharsen has been too recently introduced for comparative data to be evaluated). As between 606 and 914, however, the advantage is definitely with arsphenamine. Figure 4 shows that the prospects of "cure" are 16 per cent greater, and the prospects of clinical relapse 5 per cent less with arsphenamine than with neoarsphenamine. This variation seems to be too slight to persuade the average physician to use the technically difficult arsphenamine in place of the technically easy neoarsphenamine. Fortunately, however, it is probably true that arsphenamine results can be approximated with neoarsphenamine if larger doses and longer courses of the latter are given to compensate for its therapeutic inferiority. As a matter of fact, it is probable that satisfactory results may be obtained with any of the four arsphenamines mentioned, if they are given in adequate dosage by the continuous system and for a long enough time.

As between bismuth and mercury, the advantage is definitely with bismuth, as is shown in figure 5. Where arsphenamine plus bismuth is given serologic reversal is 12 per cent more frequent, and infectious relapse 6 per

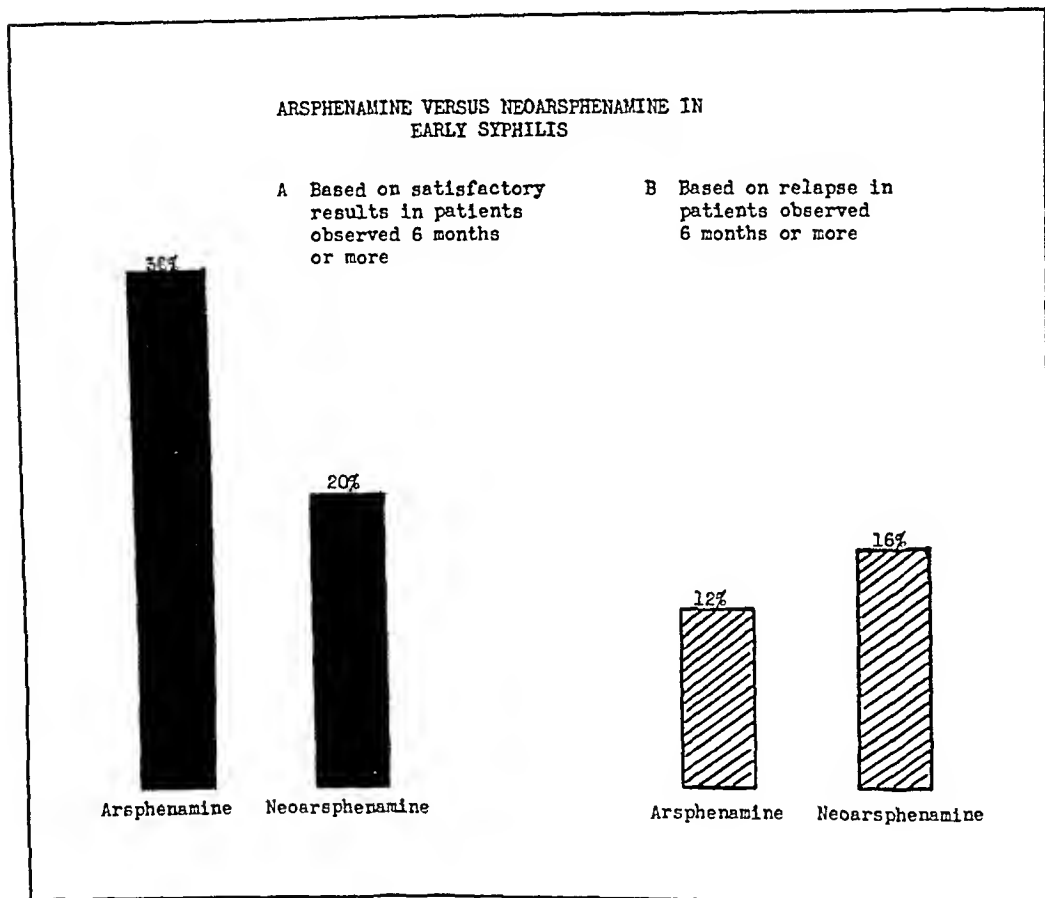


FIG 4

cent less frequent, than if the same amount of arsphenamine plus mercury is used. The bismuth preparation employed should not be, for reasons beyond the scope of this paper, water soluble, but should be liposoluble or an insoluble salt suspended in oil.

Treatment should be continuous. The reasoning which led to the adoption of this method of treatment is briefly as follows, and is based on the interplay of the biology of syphilitic infection, the mechanism of drug action, and the phenomenon of drug resistance.

Early syphilis may occasionally be "cured" by one or a few injections of an arsphenamine, with or without associated heavy metal. In the majority of patients, however, biologic "cure" does not result from a small amount of treatment. Treatment, whether adequate or inadequate, interrupts the development of resistance (or immunity) to the virus, and may actually depress it, by preventing the normal sequence of events in an un-

treated patient, i.e., gradually developing insusceptibility to reinfection, spontaneous healing of secondary lesions, spontaneous destruction of treponemes, and latency. If treatment is inadequate (or intermittent), and the patient is left, at the beginning of the first rest period, with living treponemes in his tissues, he must elaborate his immune reactions afresh against these remaining organisms. Depending on the location of the surviving organ-

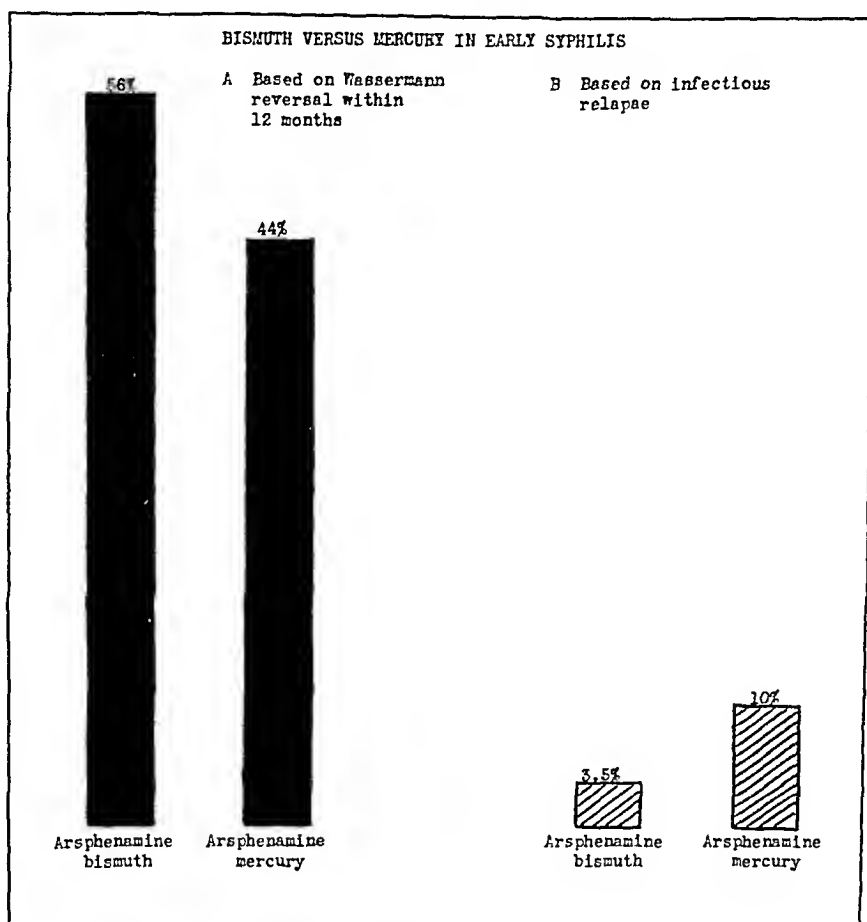


FIG 5

isms and the interval between treatment courses, he may not develop obvious clinical or serologic evidence of relapse, though some degree of biologic relapse may be expected unless the amount of treatment before the rest period has been adequate to destroy every treponeme.

If treatment is purposely intermittent, combining an arspenamine and a heavy metal in a single course, rest periods are obligatory because (1) the patient's tolerance to toxic drugs must not be exceeded, (2) experimental and clinical evidence indicates that sometimes, if not always, the organisms acquire a tolerance for the drugs employed, and become drug resistant. Under these circumstances, the obligatory rest period, leaving the patient

without the protection either of chemotherapeutic treatment or of his own defense mechanism, paves the way for relapse

With continuous treatment, on the contrary, courses of an arsphenamine may be given in alternation with courses of a heavy metal, without rest periods of any sort. Under these circumstances, the patient's tolerance for

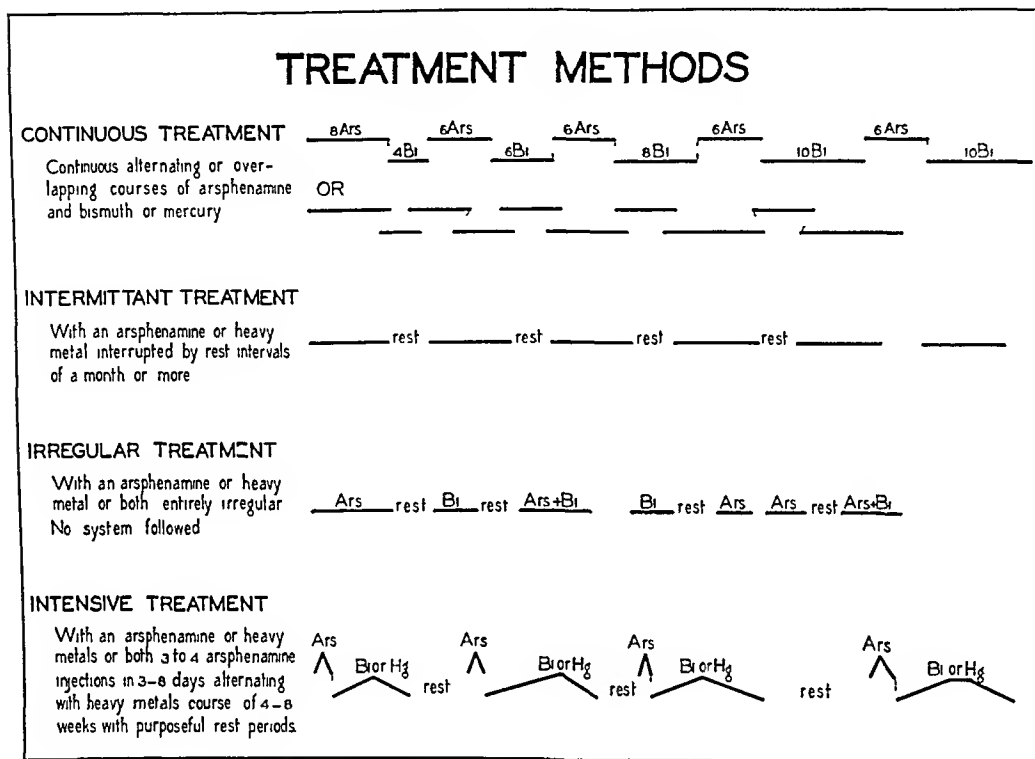


FIG 6

toxic drugs need not be exceeded, the phenomenon of drug resistant strains of organisms need not be feared (since drug resistance is usually drug specific), and most important of all, the patient's own defense mechanism is constantly augmented or replaced by the continuous effect of treponemicidal, treponemistatic, or resistance-building drugs

The test of this reasoning is, of course, the results obtainable in human beings by the use of the method. Moore and Kemp,⁶ in 1926, presented data showing the superior results of continuous over intermittent treatment, and their findings have been confirmed on a much larger scale by the Co-operative Clinical Group and by the League of Nations enquiry into syphilitic treatment. From all points of view studied, both major and minor, the treatment of early syphilis is more successful with the continuous than with any other method. Here it is necessary only to discuss briefly three of the most important points: (1) the ultimate clinical outcome, i.e., the probability of "cure", (2) the incidence of clinical relapse, and (3) serologic reversal.

The Cooperative Clinical Group studied the results of four methods of treatment, diagrammed and explained in figure 6. The continuous method accounts for 14 per cent more "cures" in all types of early syphilis and for

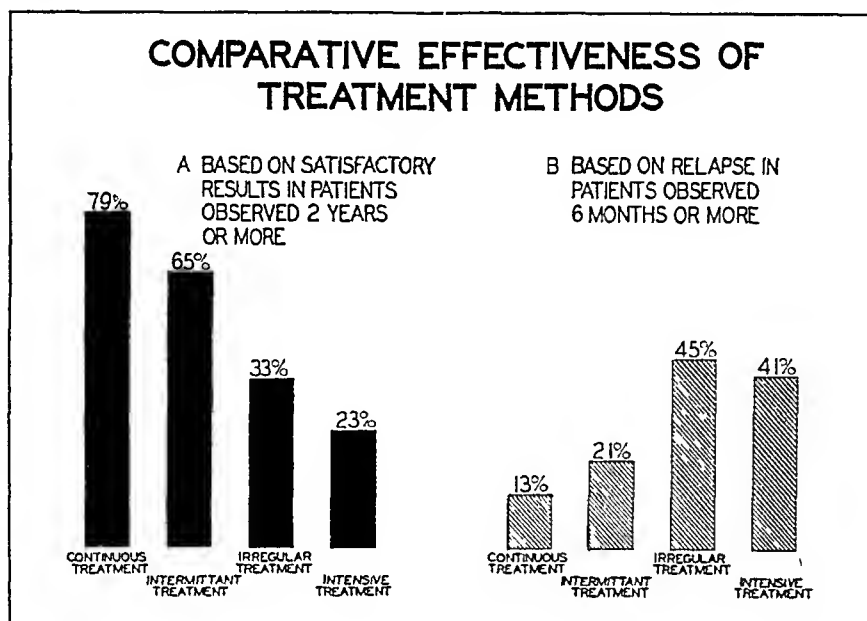


FIG 7

8 per cent less relapses, than its nearest competitor, intermittent treatment. Interestingly enough, the intensive (Pollitzer) system gave the poorest results of all, even worse than those of the most haphazard and irregular

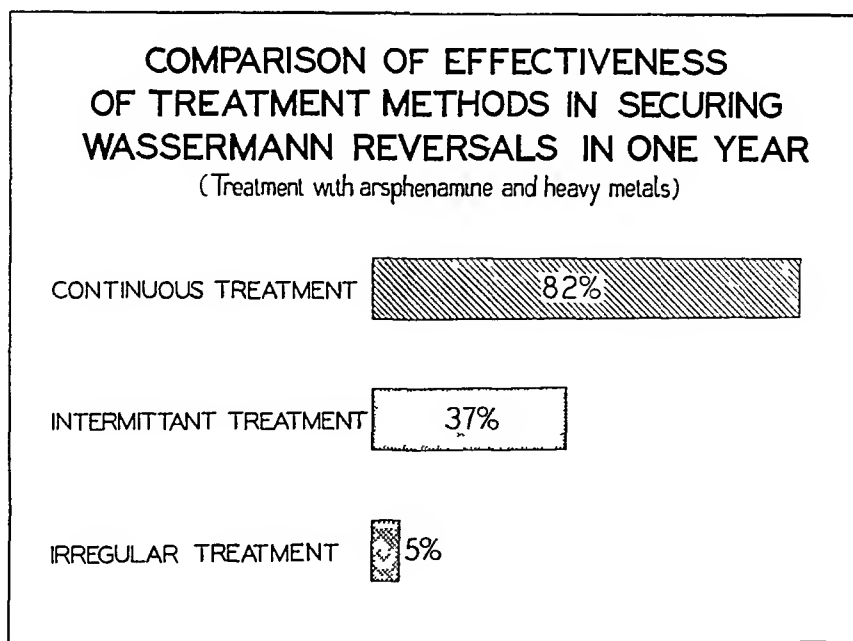


FIG 8

treatment (figure 7), a point of considerable interest in view of the revival of a modification of this idea by Chargin and his associates

The difference between the various treatment schemes in bringing about serologic reversal within a given period of time is even more striking. In figure 8 it is shown that serologic negativity was achieved within a year in 82 per cent of those treated continuously, in less than half as many when treatment was intermittent, and in only 5 per cent of those treated irregularly. The converse of this chart is the obvious fact that in early syphilis, a faulty treatment method may actually be responsible for that feature of

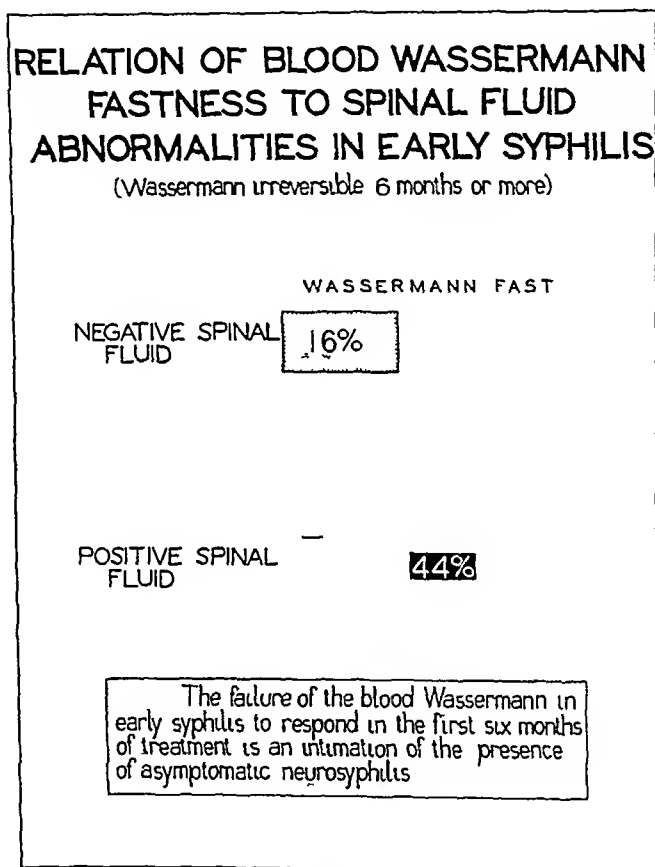


FIG 9

syphilotherapy which most disturbs the average physician, namely, Wassermann fastness

More serious still, intermittent or irregular treatment causes an increased incidence of serologic evidence of invasion of the nervous system, i.e., asymptomatic neurosyphilis. Fortunately for the patient, though not generally appreciated by the therapist, there is a close relationship between the incidence of these two factors, asymptomatic neurosyphilis and Wassermann fastness (figure 9). If in early syphilis (not true of late syphilis) the blood serologic test remains persistently positive for six months or longer, the

cerebrospinal fluid is nearly three times as likely to show evidence of neuraxis invasion as when serologic reversal has occurred. A persistently positive blood test in treated early syphilis urgently demands routine spinal fluid study. If asymptomatic neurosyphilis is present, intensification or modification of the routine treatment scheme is required.

Treatment must be prolonged to a minimum (depending on the stage of infection) of 12 to 18 months. While it is true that some patients are "cured" with much less treatment than this, there is no way in which such fortunate individuals may be recognized before or during treatment. It is essential, therefore, to give all patients enough treatment to "cure" the most resistant member of the group, even though this amount is more than some may need. The minimum duration of treatment has been arrived at on the basis of prolonged experience under rigid serologic and clinical control. The essential data justifying the standard named are presented in figure 10, which shows the approximate probability of "cure" with varying

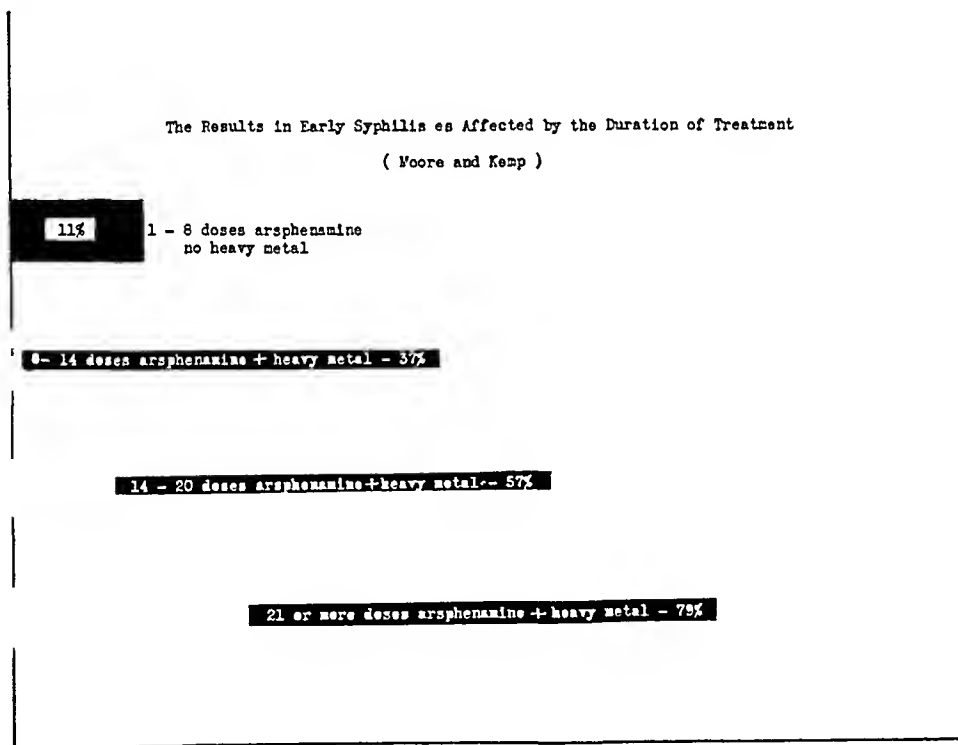


FIG 10

amounts of treatment. It must be remembered that these data are applicable only to patients with uncomplicated early syphilis, in whom the course of the disease and of treatment has been uneventful. Patients with clinical or serologic relapse, with treatment resistance, with grave treatment reactions which interfere with subsequent intensive treatment, and with asymptomatic neurosyphilis, are not included. For such persons, treatment is a

highly individualized procedure, usually demanding expert consultative advice

The optimum duration of treatment is slightly shorter if the diagnosis is made and treatment started during the seronegative primary stage, when, given a cooperative patient and no complications, "cure" is nearly certain with 12 months of continuous treatment. With seropositive primary and early secondary syphilis, 18 months of treatment are required to produce results which are not quite so certain.

The duration of treatment may be measured if desired, though preferably only by the expert, by serologic standards. On this basis, the criterion set by Keidel 20 years ago still holds good, namely, one full year of continuous treatment after serologic tests of blood and cerebrospinal fluid have become and have remained completely negative. Since the use of such a standard demands frequent repetition of serologic tests, thereby adding to the cost of treatment, and since difficulties of interpretation of such serial serologic testing confront both the inexperienced physician and his anxious patient, it is probably better for the average practitioner to discard the serologic method of treatment control and to rely on the arbitrary standard already mentioned. These standards, i.e., 12 months of continuous treatment for seronegative primary syphilis and 18 months of continuous treatment for seropositive primary or early secondary syphilis, are in fact based upon the correlation of clinical and serologic standards in thousands of patients treated under expert control.

Determination of "cure" requires lifelong post-treatment observation. There is no other criterion of "cure" in human beings. Until quite recent years it was the custom even for the expert to dismiss his well treated patient as "cured" within 1 to 3 years after the completion of treatment, and this brief observation period is still the custom of the less experienced physician. Brief thought as to the extreme chronicity of syphilis in untreated, or if treated in uncured, patients shows the advisability of prolonged follow-up. Fifteen to 20 years after infection usually elapse before the development of obvious signs of the two important late sequelae, cardiovascular and neurosyphilis. To protect one's treated patient against such disasters, a year or two of casual post-treatment observation is not enough, the patient must be followed for a life time. The treated syphilitic patient is the ideal subject for the periodic health examination.

SUMMARY

Though the adequate treatment of early syphilis is of importance from the standpoints of the individual patient, of the public health, and of the public expense, and though proved adequate treatment methods are available, they are not being generally applied.

The reason for this failure lies in part in the biology of syphilitic infection, i.e., in the fact that it is sometimes, perhaps often, symptomless in

the early stages, in part in lack of knowledge of the laity of the prevalence, characteristics, and public and individual importance of syphilitic infection, in part in the failure of the medical profession to employ adequate methods of early diagnosis and treatment. Remedies for these three faults are briefly suggested.

The modern treatment of early syphilis is based on five fundamental principles, as follows

- (1) Early diagnosis
- (2) The use of drugs of proved worth
- (3) The use of a continuous treatment system, without rest periods
- (4) The use of treatment prolonged to an arbitrary minimum of 12 to 18 months
- (5) Determination of "cure" by lifelong post-treatment observation

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GLANDERS¹

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GLANDERS, although an uncommon disease in man, is so frequently misdiagnosed, so pernicious in its manifestations and of such great importance as a public health problem when it does occur that it merits more attention than it has so far received. There are but few states that provide, in their public health laws, for the protection of their residents against this disease. Since the advent of the motor car, glanders in man has materially decreased, but in rural districts and especially in the southwestern states many cases probably go undiagnosed and constitute a genuine danger to the public health.

Strictly speaking the term glanders should be limited to the infection of the nasal mucous membrane and the internal organs, while the term farcy designates the skin and lymphatic manifestations of the same disease. In general terms glanders may be defined as a specific infectious disease due to the *Bacillus mallei*,[†] not uncommon in the horse, mule and ass and contracted by man through immediate contact with an infected animal.

Glanders may be either acute or chronic. The acute type is very frequently devastating in the rapidity of its evolution and often takes the form of a septic pneumonia secondary to a primary nasal mucous membrane infection. It is often mistaken for general sepsis, the nature of the primary lesion passing unrecognized. The acute cases are usually fatal and from a public health point of view not as important as the chronic type.

Chronic glanders presents no characteristic symptomatology. The essential lesion is an infectious granuloma that breaks down, as a rule, rather rapidly with the formation of slow healing ulcers in the skin and mucous membranes and deep seated abscesses in internal organs, muscles and other parts of the body. Bone infections have been noted. In cases where the virulence of the infecting organism is low, there is considerable epithelioid cell formation and also giant cell production. This type of lesion is not unlike a tubercle. These patients present symptoms of a chronic septic character with intervals of remission that may be short or long. A very few recover, the majority succumb to an acute exacerbation usually with acute pulmonary manifestations.

The two cases I have to report are of the chronic insidious type with no initial acute manifestations. The first case was under observation but a short time, while the second one has been observed for over five years.

* Received for publication June 1, 1935.

[†] *Actinobacillus mallei*

CASE REPORTS

Case 1 A white female, aged 36 Her previous history is irrelevant except that she was reared on a farm and that she came into intimate contact with two horses that died of an unknown disease 18 months previous to her present examination Shortly after the death of the above mentioned horses she first noticed a slight nasal discharge followed shortly by the formation of an ulcerated patch on the tip of the nose The nasal discharge gradually increased and became mucopurulent, while the skin lesions advanced until the entire upper lip and nose presented an ulcerated, discharging mass She consulted a number of physicians and the diagnosis varied from syphilis and tuberculosis to epithelioma At no time did she suffer from marked constitutional symptoms At the time of examination the patient was well nourished and the physical examination revealed no abnormalities except as portrayed in figure 1



FIG 1 The glanders lesions of the nose and lip in case 1

The temperature, blood count and urine examination were all normal The blood Wassermann was negative Tests for the tubercle bacillus were negative and tissue examination revealed no malignancy (Figure 2) There were no laryngeal symptoms The skin lesions were covered with a thick, yellowish crust which after removal revealed many small ulcerations on a surface of granulating tissue Smears from the discharge from the nose and from the skin ulcerations revealed a mixed infection with many gram-negative, slightly curved rods This organism proved to be *Bacillus mallei*, and the patient's blood agglutinated a known organism in dilutions up to 1-160 Treatment with an autogenous vaccine, together with such local treatment as was indicated, was instituted, but the patient refused to remain under my care and the eventual outcome in this case is not known

Case 2 A Mexican youth, aged 15, presented himself for treatment because of the loss of sight in one eye, a severe infection in the other eye, a mucopurulent discharge from the nose and extensive ulceration of the nose and upper lip as shown in figure 3

His previous history was irrelevant except that he had come into intimate contact with a horse that had died from some unknown disease shortly before he became ill. The patient stated that the disease manifested itself first by a redness and discharge from the lower lid of the left eye. One and one-half years later this was followed by a discharge from the nose and ulcerations of the tip of the nose that gradually spread to the upper lip. He next noticed some slight hoarseness and difficulty in swallowing. About six months previous to his present examination (July 1929), his right eye became infected. At no time did he suffer any constitutional

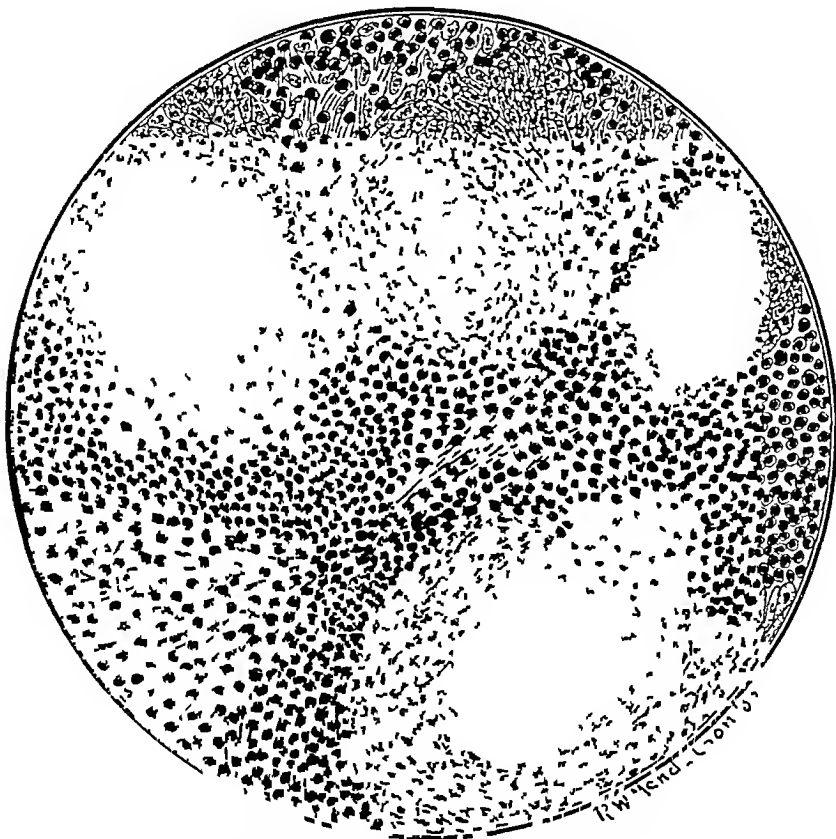


FIG 2 Section from case 1, showing granulomas made up of masses of epithelioid cells with central necrosis. There is abundant leukocytic infiltration. No giant cells are to be seen in this section.

symptoms. On physical examination he presented an emaciated body, considerable enlargement of all of the glands in the neck, a normal blood count, a negative Wassermann and a normal urine examination. The right eye showed considerable corneal ulceration with a high degree of conjunctival inflammation. The left eye presented old corneal ulcers, moderate conjunctival inflammation and considerable mucopurulent discharge. There were no ulcers in the oral cavity, the membranes were injected and there was a well marked nasopharyngeal discharge. The external nasal passages were blocked with encrusted, yellowish deposit (Figure 3). The skin lesions were covered with a thick, encrusted mass of discharge that involved the



FIG 3 Case 2, before treatment



FIG 4 Case 2, six months after treatment with autogenous vaccine

mucous membrane of the upper lip to the gum line. Removal of the crusts revealed an ulcerating, granulomatous tissue from which was obtained a mixed infection with many gram-negative, slightly curved rods that proved to be *Bacillus mallei*. This patient's blood agglutinated a known culture in a dilution of 1-160. Treatment of this case consisted of various local treatments and autogenous vaccine. The condition of



FIG 5 Case 2, three years after vaccine treatment

the patient six months after treatment is well defined in the illustration (figure 4). After this period of treatment the patient left my service and I did not see him for a period of about two years when he returned and his condition at that time is well portrayed (figure 5). He also has developed in the meantime a large ulceration on the left elbow from which *B. mallei* can be recovered.

COMMENT

The diagnosis in these cases is of course suggested by the history, the characteristic nasal discharge and the ulcerations. Differential diagnosis must take into consideration epithelioma, syphilis and tuberculosis. In the tropics one must also consider the possibilities of a framboesial infection.

These diseases are not difficult to eliminate. Agglutination tests are of primary importance in confirming the diagnosis, and one may either agglutinate the patient's serum against a known organism or, having isolated the specific organism from the patient's lesions, agglutinate it against a known serum.

Regarding the treatment one must not be too optimistic. Apparent cure is often followed by relapse and not infrequently a case will subside without the benefit of medication. Watson of Canada reports good results with the use of hyperimmune serum, but this is difficult to obtain. Autogenous vaccine with indicated local treatment has been my choice, and in view of the tendency to relapse in spite of apparent cure it is advisable to keep these patients under observation for many years. They are at all times a danger to the public health during the active stages of the disease and should be under strict quarantine. While enjoying periods of inactivity they should report at frequent intervals for observation.

THE LOCALIZATION OF SUPRATENTORIAL TUMORS OF THE BRAIN BY OLFACTORY TESTS

By CHARLES A. ELSBERG, M.D., *New York, N. Y.*

IN a series of papers published in the Bulletin of the Neurological Institute of New York (1935, 1936) new quantitative procedures for the examination of the olfactory sense were described. One of the procedures was called *blast injection of odors* and consists of the injection of measured volumes of odor into one or both nasal passages during short periods of voluntary cessation of breathing. In this procedure the pressure under which the blast of odor is released into the nose takes the place of the force of the ordinary inspiratory movement.

The smallest number of cubic centimeters of an odor that can normally be identified by the blast injection test was called the MIO (minimum identifiable odor) of the odorous substance. The MIO of any one substance was found to have about the same value in all normal individuals.

A second method was called *stream injection of odors*. In this procedure a continuous stream of odor is injected into one or both nasal passages for a period during which the individual who is being examined breathes through the mouth. The stream injection of odors was used to produce olfactory fatigue and to study the trigeminal effects of odors. Here again it was found that the duration of olfactory fatigue for any odor produced by stimulation of the olfactory receptors was about the same in all normal individuals. The effects of blast injection and stream injection of a variety of odors were investigated in a large series of healthy individuals, and information was gained regarding the nature of the olfactory stimulus, the relative importance of pressure and volume of the olfactory stimulus for the olfactory impulse, the physiological aspects of monorhinal, binorhinal and bisynchronorhinal smell, and the nature of and organic basis for olfactory fatigue.

Finally two odorous substances—coffee and citral—were selected for clinical tests of the sense of smell. These two substances were chosen because their odors are familiar, and because the odor of one of them—coffee—is a pure olfactory stimulant, while that of citral affects both the olfactory and the trigeminal nerves. Several years were spent in the study of the sense of smell in normal individuals. Finally, in order to learn whether the methods were of value for the localization of tumors of the brain, the tests were used in patients in whom an intracranial neoplasm was suspected.

Up to the present time, we have examined 118 patients in whom an intracranial growth was suspected or considered a possibility. In 52 of the cases,

* Read by invitation at the meeting of the American College of Physicians, Detroit, Michigan, March 2, 1936.

the situation of a neoplasm was verified by operation, autopsy or by pneumography. These 52 cases form the basis for this report.

In order that the reader can appreciate the results and the significance of the tests, it is necessary to give a short description of the procedures called *blast injection* and *stream injection of odors*. The apparatus and methods have been described in detail in other publications.

For our present purpose it will suffice to explain that after the M I O of each side of the nose had been determined, the duration of olfactory fatigue produced by the stream injection of the odors for 30 seconds at a volume-rate of 2000 c c to the minute was established for each side of the nose.

The presence of gross abnormalities in the nasal passages was first excluded by the Zwaardemaker test. Then blast injections of the odor of coffee were given into one nasal passage at intervals of 30 seconds until the smallest volume of odor that could be identified at three successive blast injections was determined. After the value of M I O of one side had been found and the patient had been given a few minutes of rest, the M I O of the other side was determined by blast injections. Then, again after a few minutes of rest, the patient was given a stream injection of coffee odor into the nasal passage that had been tested first. The duration of the ensuing olfactory fatigue was established by giving, every 30 seconds, blast injections of the volume that had been necessary for M I O, until the ability to identify the odor as coffee had returned. After another rest period, the procedure was repeated on the other side of the nose. Later, similar blast injection and stream injection tests were made with citral. By these procedures the M I O and the duration of olfactory fatigue on each side for coffee and for citral were established.

TABLE I
The Determination of M I O for Coffee in Case 1
Blast injections of coffee odor given every 30 seconds into

Right Side (c c)	Left Side (c c)
8 - + *	8 - +
8 - 0	8 - +
8 - 0	8 - +
9 - 0	7 - +
9 - 0	7 - +
11 - 0	7 - +
13 - 0	6 - +
15 - 0	6 - 0
15 - 0	6 - 0
16 - 0	7 - +
17 - +	7 - + = M I O
17 - +	
17 - +	
16 - 0	
16 - 0	
17 - + = M I O	

* + = odor identified, 0 = odor not identified

The number of blast injections required in a patient before the M I O for coffee of each nasal passage had been obtained is shown in table 1. The table illustrates the steps of the procedure by which M I O is established.

Table 1 shows that on the right side 17 c c were the smallest number of c c that were identified on three successive blast injections into the right nasal passage, and 17 was therefore the M I O on the right side. Similarly 7 was the M I O on the left side.

Sometimes, as in the instance above given, the M I O can be established by a relatively small number of blast injection tests, at other times a larger number of blast injections has to be given before the examiner is certain that he has obtained the correct values for the M I O. Because the injections of volumes of odor corresponding to M I O are used in order to determine the duration of olfactory fatigue, it is important that in the preliminary blast injection tests the volume necessary for M I O be accurately determined.

THE CHARACTER OF THE CHANGES FOUND BY THE OLFACTORY TESTS AND THEIR SIGNIFICANCE FOR LOCALIZATION OF THE GROWTH

In order that the significance of the figures obtained in patients with tumors of the brain may be appreciated, a table of the results of tests in a few healthy individuals is given (table 2). In this table the duration of fatigue is the number of minutes which elapsed after a stream injection of the odor for 30 seconds at a volume-rate of 2000 c c per minute, before the odor was again identified.

TABLE II
The Normal M I O and the Duration of Fatigue in 6 Normal Individuals

Name	Coffee				Citral			
	M I O		Duration of Fatigue		M I O		Duration of Fatigue	
	Right	Left	Right (min)	Left (min)	Right	Left	Right (min)	Left (min)
V O	9	9	2	2	8	8	2.5	3
J B D	8	8			7	7	2.5	2.5
C C H	8	8	2	2	7	7	2.5	2.5
H G E	7	7	2.5	2.5	6	6	2.5	3
C A E	9	8	1.5	2	8	8	2	2.5
F H	8	8	2	2	7	7	2	2.5

A few examples of the olfactory records of patients and the interpretation of the results of the tests are given in what follows.

Case 1 V F Aneurysm of right internal carotid artery

Clinical Symptoms Loss of vision in right eye with primary optic atrophy of that side

Roentgen-Ray Examination Probable aneurysm of right carotid artery

Olfactory Tests

Coffee			Citral	
M I O Right 17 Stream Injection for 30 sec Return of M I O	M I O Left 7 Stream Injection for 30 sec Return of M I O		M I O Right 16 Stream Injection for 30 sec Return of M I O	M I O Left 7 Stream Injection for 30 sec Return of M I O
17 - + * (*)	7 - + *	30"	16 - 0	7 - + *
17 - +	7 - +	1'	16 - + *	7 - +
17 - +	7 - +	1'30"	16 - +	7 - +
17 - +		2'	16 - +	6 - 0

(*) In all of the cases * indicates the duration of fatigue

Result of Olfactory Tests

M I O elevated on right, normal on left

Duration of fatigue not prolonged on right and left

Conclusion An extracerebral lesion on the right side compressing the right olfactory nerve

Case 2 B B Pituitary adenoma

Clinical Symptoms Primary optic atrophy with loss of vision in right eye, temporal hemianopsia on left

Roentgen-Ray Examination Extensive enlargement and destruction of sella turcica

Olfactory Tests

Coffee			Citral	
M I O Right 30 = 0 Stream Injection for 30 sec Return of M I O	M I O Left 18 Stream Injection for 30 sec Return of M I O		M I O Right 18 Stream Injection for 30 sec Return of M I O	M I O Left 13 Stream Injection for 30 sec Return of M I O
	18 - 0	30"	18 - 0	13 - +
	18 - 0	1'	18 - + *	13 - ±
	18 - 0	1'30"	18 - ±	13 - ±
	18 - + *	2'	18 - +	13 - + *
	18 - +	2'30"	18 - +	13 - +
	18 - +	3'	18 - +	13 - +

Result of Olfactory Tests

M I O elevated on right and left but higher on right

Duration of fatigue not prolonged

Conclusions An extracerebral lesion that is involving both extracerebral olfactory pathways, the right more than the left

Case 3 I S Mesial sphenoid ridge meningioma

Clinical Symptoms Primary optic atrophy with loss of vision of right eye

Roentgen-ray of skull negative

Olfactory Tests

Coffee			Citral	
M I O Right 30 Stream Injection for 30 sec Return of M I O	M I O Left 6 Stream Injection for 30 sec Return of M I O		M I O Right 35 Stream Injection for 30 sec Return of M I O	M I O Left 4 Stream Injection for 30 sec Return of M I O
30 - 0	6 - + *	30"	35 - + *	4 - 0
30 - + *	6 - +	1'	35 - +	4 - 0
30 - +	6 - +	1'30"	35 - +	4 - 0
30 - +		2'		4 - + *
		2'30"		4 - +
		3'		4 - +

Result of Olfactory Tests

M I O elevated on right, M I O on left low

Duration of fatigue not prolonged

Conclusion Direct pressure on right extracerebral olfactory pathways by a small lesion which must have existed for a considerable time because there is compensatory hyperacuity of smell on the left side

Case 4 G M Deep left frontal astrocytoma

Clinical Symptoms History of transient left hemiplegia six years before, occasional generalized convulsive seizures Reflexes Right equal left Early papilledema

Roentgen-ray showed calcified tumor in left frontal lobe

Olfactory Tests

Coffee			Citral	
M I O Right 7 Stream Injection for 30 sec Return of M I O	M I O Left 11 Stream Injection for 30 sec Return of M I O		M I O Right 4 Stream Injection for 30 sec Return of M I O	M I O Left 8 Stream Injection for 30 sec Return of M I O
7 - 0	11 - 0	30"	4 - + Faint	8 - 0
7 - + Faint *	11 - 0	1'	4 - 0	8 - + Faint
7 - +	11 - 0	1'30"	4 - + Faint	8 - 0
7 - +	11 - + Faint	2'	4 - 0	8 - ?
7 - +	11 - 0	2'30"	4 - 0	8 - 0
7 - +	11 - 0	3'	4 - + Faint	8 - 0
	11 - 0	3'30"	4 - 0	8 - + Faint
	11 - 0	4'	4 - + *	8 - 0
	11 - 0	4'30"	4 - +	8 - 0
	11 - 0	5'	4 - +	8 - 0
	11 - 0	5'30"		8 - + Faint
	11 - + *	6'		8 - 0
	11 - +	6'30"		8 - 0
	11 - +	7'		8 - + *
		7'30"		8 - +
		8'		8 - +
		8'30"		7 - 0

Result of Olfactory Tests

M I O elevated on left Fatigue prolonged on left

Conclusion Left frontal tumor near under surface of frontal lobe

Case 5 C H Right parietal lobe glioma

Clinical Symptoms Marked motor and sensory disturbances on left side of body, papilledema

Roentgen-ray shows calcified tumor in right parietal lobe

Olfactory Tests

Coffee			Citral	
M I O Right 5 Stream Injection for 30 sec Return of M I O	M I O Left 5 Stream Injection for 30 sec Return of M I O		M I O Right 4 Stream Injection for 30 sec Return of M I O	M I O Left 4 Stream Injection for 30 sec Return of M I O
5 - 0	5 - 0	30"	4 - 0	4 - 0
5 - 0	5 - 0	1'	4 - + ?	4 - 0
5 - 0	5 - 0	1' 30"	4 - 0	4 - 0
5 - 0	5 - 0	2'	4 - 0	4 - 0
5 - 0	5 - + *	2' 30"	4 - 0	4 - 0
5 - 0	5 - +	3'	4 - +	4 - + *
5 - 0	5 - +	3' 30"	4 - 0	4 - ±
5 - +		4'	4 - 0	4 - +
5 - 0		4' 30"	4 - +	4 - +
5 - 0		5'	4 - 0	
5 - + *		5' 30"	4 - 0	
5 - +		6'	4 - + *	
5 - +		6' 30"	4 - +	
		7'	4 - +	

Result of Olfactory Tests

Low M I O indicates increased intracranial pressure

Duration of fatigue normal on left, prolonged on right

Conclusion Right hemisphere tumor—not deep

These records illustrate some of the results of olfactory tests made in patients with verified tumors of the brain. The analysis of the results in the 52 cases which form the basis for this paper has permitted us to draw the following conclusions:

1 *In subfrontal extracerebral growths, the M I O on one or both sides is elevated, while the duration of olfactory fatigue is not prolonged.* If the neoplasm is small and is entirely unilateral, the elevation of M I O is found only on the same side, if the growth is large, the M I O may be raised on both sides and the greater elevation of M I O is found on the side on which the growth or the larger part of the growth is situated. Thus in small aneurysms of the internal carotid artery and mesial sphenoid ridge meningiomas, the M I O is elevated on the affected side and normal on the other side. In the case of a larger aneurysm or tumor, the M I O is elevated bilaterally. Meningiomas attached to the dura of the cubiform plate of the ethmoid or of the tuberculum sellae produce a bilateral elevation of M I O. In pituitary tumors that have not extended through the diaphragm of the sella, the M I O is normal, but as soon as the growth has become suprasellar, pressure is exerted upon the extracerebral olfactory pathways and the M I O is elevated unilaterally or bilaterally.

Case 6 Deep left hemisphere glioma

Clinical Symptoms For 8 months vague disturbances of left upper extremity Examination shows hyperactive tendon reflexes on left papilledema of 4 diopters, bitemporal hemianopsia

Ventriculography Lateral and third ventricles displaced to right

Olfactory Tests

Coffee			Citral	
M I O Right 4 Stream Injection for 30 sec Return of M I O	M I O Left 6 Stream Injection for 30 sec Return of M I O		M I O Right 5 Stream Injection for 30 sec Return of M I O	M I O Left 5 Stream Injection for 30 sec Return of M I O
4 - + *	6 - +	30"	5 - 0	5 - 0
4 - +	6 - 0	1'	5 - + *	5 - 0
4 - +	6 - 0	1' 30"	5 - +	5 - +
	6 - 0	2'	5 - +	5 - 0
	6 - +	2' 30"		5 - +
	6 - +	3'		5 - 0
	6 - 0	3' 30"		5 - 0
	6 - + *	4'		5 - +
	6 - +	4' 30"		5 - ?
	6 - +	5'		5 - +
	6 - +	5' 30"		5 - 0
		6'		5 - +
		6' 30"		5 - 0
		7'		5 - + *
		7' 30"		5 - +
		8'		5 - +

Result of Olfactory Tests

M I O low for coffee and for citral

Duration of fatigue prolonged on left

Conclusion Increased intracranial pressure

A deep intracerebral tumor in the left cerebral hemisphere

2 In supratentorial tumors within the substance of one cerebral hemisphere the M I O may be normal or smaller than normal, but the duration of homolateral fatigue is definitely prolonged Apparently the degree to which the duration of olfactory fatigue is prolonged depends upon the extent to which the neoplasm involves deeper parts of the brain The more deeply a tumor is situated, the longer is the duration of the fatigue produced by the procedure If the fatigue lasts more than ten minutes, the growth extends to near the midline or actually lies in the midline

3 In tumors in the substance of one frontal lobe, the M I O is elevated and olfactory fatigue is prolonged on that side The elevation of M I O is due to pressure upon the extracerebral olfactory pathways of the same side as the growth Therefore the combination of elevation of M I O and prolonged duration of fatigue must mean that the neoplasm is in the corresponding frontal lobe

4 In patients with increased intracranial pressure due to tumors of the brain, there is frequently an increased irritability of the olfactory pathways,

Case 7 Glioblastoma multiforme in left frontal lobe extending across midline into right frontal lobe

Clinical Symptoms Four weeks' history of right hemiparesis and papilledema

Olfactory Tests

Coffee			Citral	
M I O Right 11 Stream Injection for 30 sec Return of M I O	M I O Left 26 Stream Injection for 30 sec Return of M I O		M I O Right 10 Stream Injection for 30 sec Return of M I O	M I O Left 25 Stream Injection for 30 sec Return of M I O
11 - +	26 - 0	30"	10 - 0	25 - 0
11 - 0	26 - 0	1'	10 - 0	25 - 0
11 - 0	26 - 0	1' 30"	10 - 0 ?	25 - 0
11 - 0	26 - 0	2'	10 - + *	25 - 0
11 - 0	26 - 0	2' 30"	10 - +	25 - 0
11 - 0	26 - 0	3'	10 - +	25 - 0
11 - 0	26 - 0	3' 30"		25 - 0
11 - +	26 - 0	4'		25 - ±
11 - 0	26 - 0	4' 30"		25 - 0
11 - 0	26 - 0	5'		25 - +
11 - 0	26 - 0	5' 30"		25 - 0
11 - +	26 - 0	6'		25 - 0
11 - 0	26 - 0	6' 30"		25 - 0
11 - 0	26 - 0	7'		25 - +
11 - 0	26 - 0	7' 30"		25 - 0
11 - 0	26 - 0	8'		25 - 0
11 - 0	26 - ±	8' 30"		25 - 0
11 - + *	26 - 0	9'		25 - + *
11 - +	26 - 0	9' 30"		25 - ±
11 - +	26 - 0	10'		25 - +

Result of Olfactory Tests

M I O elevated on both sides, left more than right

Fatigue prolonged on both sides for coffee and on left for citral

Conclusions A deeply situated tumor in the left frontal lobe near the midline The growth has probably extended also into the right frontal lobe

which is shown by values of M I O smaller than the normal While low M I O is often seen in patients with increased intracranial pressure, it does not follow that low M I O always means increased tension within the cranial chamber Low M I O's were frequently observed in diseases of the brain in which there was no increase of intracranial pressure On the other hand, in patients with papilledema and other evidences of increased pressure, the M I O may be within normal limits

The study of the sense of smell by the blast injection and the stream injection of odors is therefore of value for the localization of supratentorial tumors of the brain In some instances the olfactory tests did not show any evidence of a localized lesion and in these instances it was possible to conclude that the patient did not have a supratentorial neoplasm A more extended experience may show that the tests are of value for diagnosis as well as for localization, but up to the present time, the tests should be used

only for the localization of tumors of the brain. When employed for this purpose, the new olfactory tests may give information which may not be obtained by clinical examination. In unlocalized tumors of the brain, it is possible from olfactory tests to determine that a growth is in or under one or other frontal lobe, and if the growth is not frontal, whether it is in the right or left cerebral hemisphere. In the near future a procedure will be described by which tumors in or under one or other temporal lobe can be localized by olfactory tests.

ERRORS IN THE CLINICAL APPLICATION OF ELECTROCARDIOGRAPHY

By WILLIAM B BREED, M D , F A C P , and JAMES M FAULKNER, M D ,
F A C P , *Boston, Massachusetts*

THE last twenty years have seen an enormous growth in the use of the electrocardiograph as a diagnostic instrument. From a cumbersome and expensive machine available only to the larger hospitals and clinics have been developed models which are light enough and cheap enough to be entirely practicable for use in office or home. It is estimated that there are three thousand electrocardiographs in active use in this country today and the number of instruments is rapidly increasing. A result of this tremendous growth has been that we as internists are being called upon more and more to assess the clinical significance of electrocardiographic abnormalities.

When one examines the body of data on which much of our diagnostic and prognostic criteria in electrocardiography rest, one is struck by the paucity of suitable control material. Quite naturally most of the studies which have been made in this field were carried out on patients who came to a clinic because of suspected heart disease. The due prognosis which soon came to be associated with many electrocardiographic signs was therefore based in part on statistics from a selected group heavily weighted with bad risks. The very fact that an electrocardiogram was taken usually meant that the patient had either symptoms or signs suggestive of heart disease.

One example of overemphasis of the seriousness of an electrocardiographic finding has been in the case of bundle branch block. In the beginning we were inclined to assign a bad prognosis to every case exhibiting this sign, but as the years have gone by we have seen more and more patients with bundle branch block outliving their brief expectancy of life by many years. Although such signs of course merit serious consideration, our experience has made us more cautious about attaching prognostic significance to isolated electrocardiographic abnormalities.

From the point of view of negative evidence it has been recognized from its earliest application to clinical diagnosis that the electrocardiogram may be normal in the presence of obvious organic heart disease and consequently the importance of negative records has been duly discounted.

The subject of this paper deals with the occurrence of certain positive abnormalities—perhaps better termed peculiarities—of the electrocardiogram in the absence of organic heart disease. The importance of these peculiarities lies in the fact that they may simulate changes associated with serious cardiac disorders and thus may lead to grave diagnostic error. We

* Presented at the Detroit meeting of the American College of Physicians, March 3, 1936

do not include in this discussion the alterations in the electrocardiogram dependent on infections, toxemia or anoxemia

Abnormalities in the contour of the electrocardiogram result from abnormal relationships between the pathways of conduction and the recording electrodes. Therefore, in addition to intrinsic lesions of the conducting system and myocardium, unusual positions of the heart in the chest may be reflected in peculiar electrocardiographic patterns

RIGHT AXIS DEVIATION

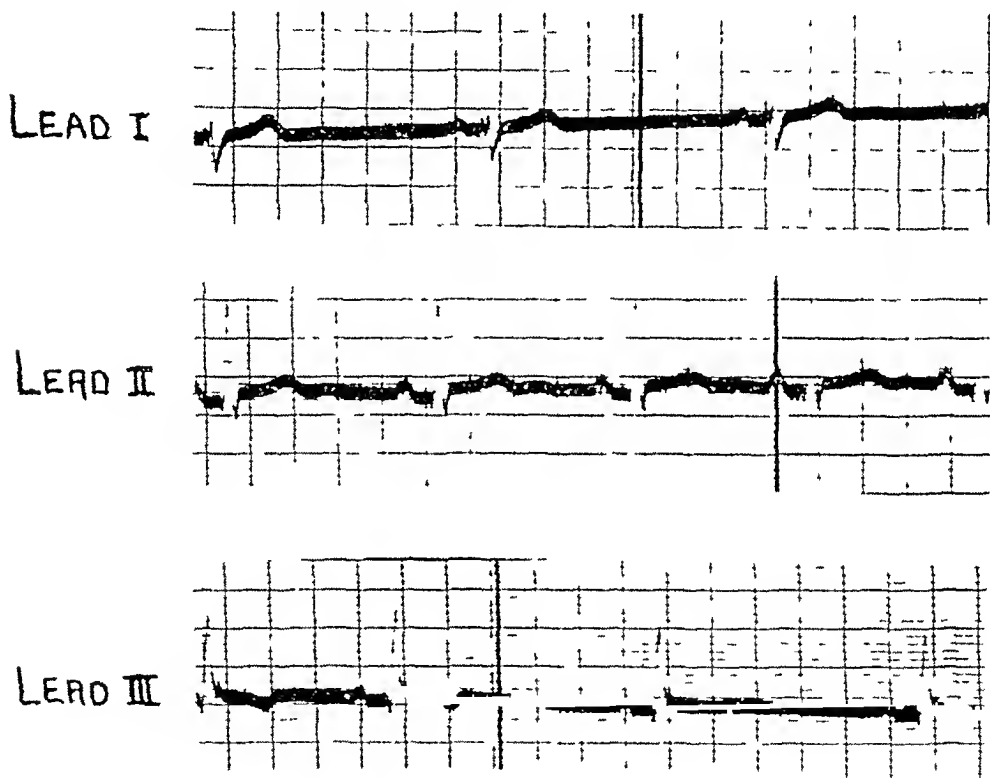


FIG 1 Right axis deviation in a normal vertical heart

The effect of position of the heart on the electrical axis has been too well recognized to require more than passing comment. Figure 1 is a record of an individual with a normal heart in a vertical position. It shows right axis deviation.

Figure 2 shows left axis deviation resulting from a transverse position of the heart in a normal, healthy young man of sthenic habitus. Deep inspiration swings the electrical axis into the normal zone. Less well recognized is the fact that high diaphragm may cause the development of a deep Q-wave and an inverted T-wave in Lead III.

In rare cases the position of the heart may determine the direction of the

T-wave in Lead II The following case, presented through the courtesy of Dr Howard B Sprague, illustrates this condition

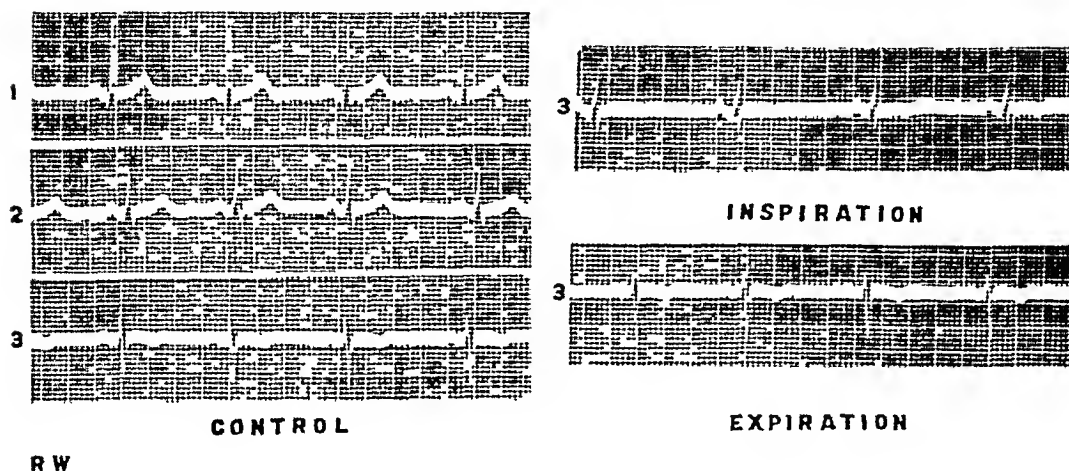


FIG 2 Left axis deviation in a normal transverse heart Note shift in axis to normal with depression of the diaphragm in inspiration

G C, a 19 year old boy, was referred to him in December 1935 because on routine examination as a college freshman he was found to have tachycardia and hypertension His past history was irrelevant He played football in high school He had no symptoms of any sort

Physical examination in general was negative The heart was not enlarged The action was rapid with marked sinus arrhythmia No murmurs were heard Blood pressure was 135 mm Hg systolic, 90 mm Hg diastolic Roentgen-ray examination showed the heart to be normal in size, shape and position

Figure 3 illustrates the marked effect of change in position of the heart on the T-waves particularly in Lead II On deep expiration the T-waves previously inverted became upright Because of its peculiar lability and in the absence of any other evidence of heart disease it was concluded that the inversion of the T-wave in Lead II did not signify myocardial disease and the boy was allowed to resume full activity

Another type of electrocardiographic peculiarity is caused by nervous influences upon intraventricular conduction The first case of this type was reported by Dr Frank N Wilson¹ of Ann Arbor in 1915 A group of them which correspond to a fairly distinctive pattern were described by Wolff, Parkinson and White² in 1930 and have come to be known by the term "functional bundle branch block" This condition is characterized by a very short P-R interval and prolonged intraventricular conduction with slurring of the initial phase of the ventricular complex The mechanism appears to be dependent upon a certain amount of vagal tone and may be abolished by atropine, adrenalin or exercise Clinically it is usually associated with a history of paroxysmal tachycardia but with no other cardiac

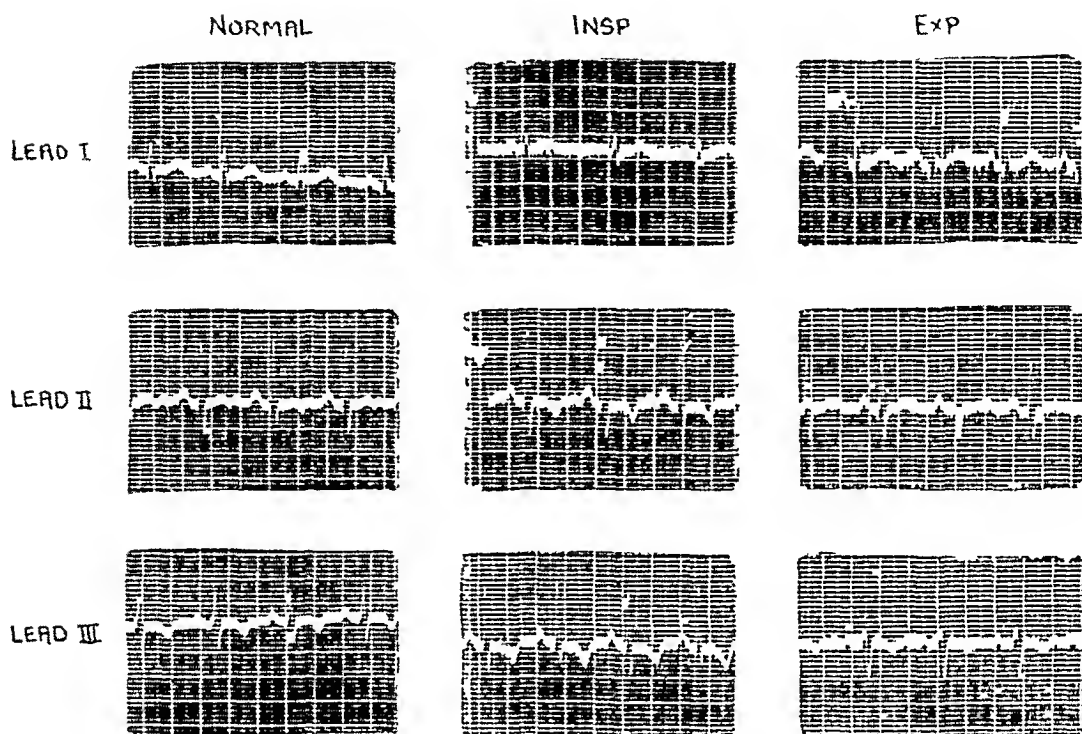


FIG 3 Peculiar T-wave in Lead II markedly altered by deep breathing Apparently normal boy

abnormality Figure 4 is an illustration of functional bundle branch block in an Italian laborer of thirty-five He gave the characteristic history of frequent attacks of paroxysmal tachycardia but no other evidence of heart disease The records were taken a few days apart and show the characteristic features of the condition in the one record and an entirely normal picture in the other In some subsequent records these changes are seen to appear and disappear within a few seconds

Figure 5 illustrates a closely similar condition with a short P-R interval and prolonged intraventricular conduction It is from a patient of Dr Paul D White

When first seen he was an 18 year old boy and a member of a college freshman swimming team He had a history of paroxysmal tachycardia Physical examination was negative except for reduplication of the first sound at the apex of the heart Roentgen-ray revealed no abnormality in the size, shape, or position of the heart and the basal metabolic rate was normal An electrocardiogram taken in 1936, eight years later, showed the same abnormalities and the same decrease in the amplitude of the T-waves after exercise

In a third group of cases transient inversion of the T-waves in Leads I and II without other changes has been observed in the absence of organic heart disease As Graybiel and White³ pointed out, this is often associated with neuro-circulatory asthenia, paroxysmal tachycardia or thyrotoxicosis

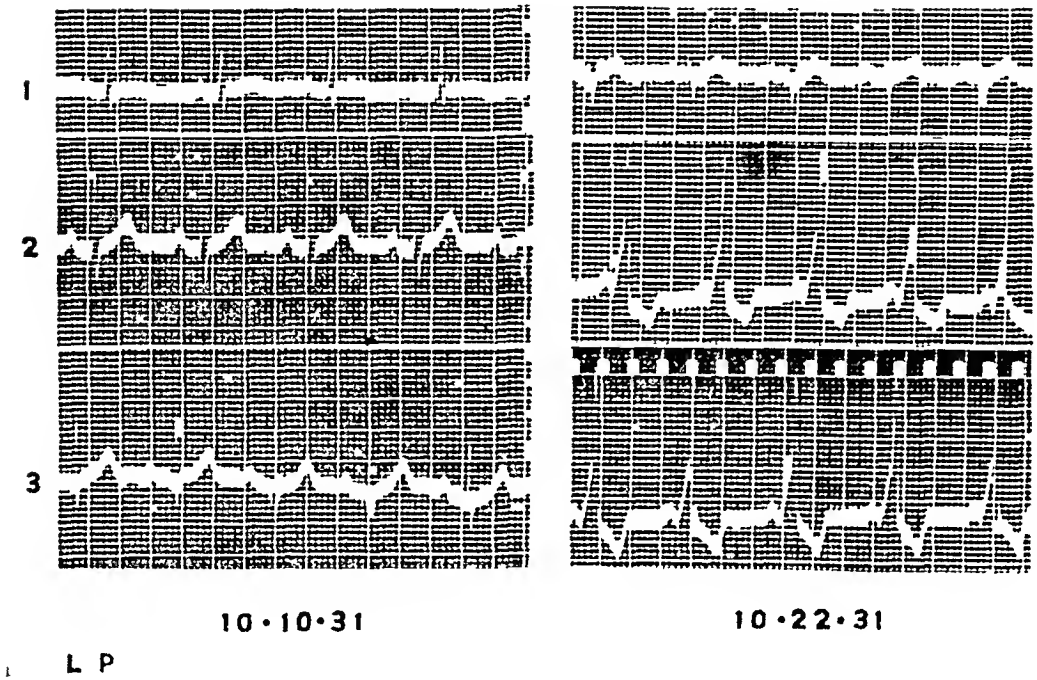


FIG 4 Normal mechanism and "functional bundle branch block" in the same individual

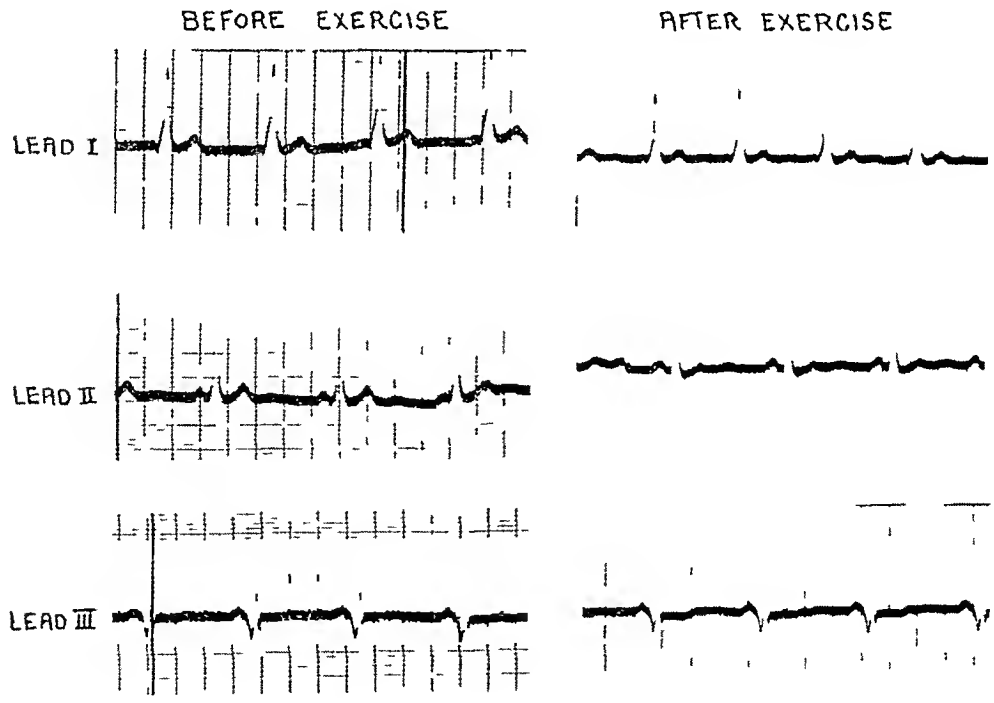


FIG 5 Intraventricular block with short P-R interval in an apparently healthy youth

The following case is an illustration of this type of disturbance

In the fall of 1934, A. P., a 16 year old boy, had presented himself with the story that his local doctor had forbidden him strenuous exercise because of rapid heart action. He himself sometimes felt his heart pound but not particularly when active. He did not know whether the action was rapid or irregular. He had no other complaints. He had had a normal development without rheumatic fever, scarlet fever or chorea.

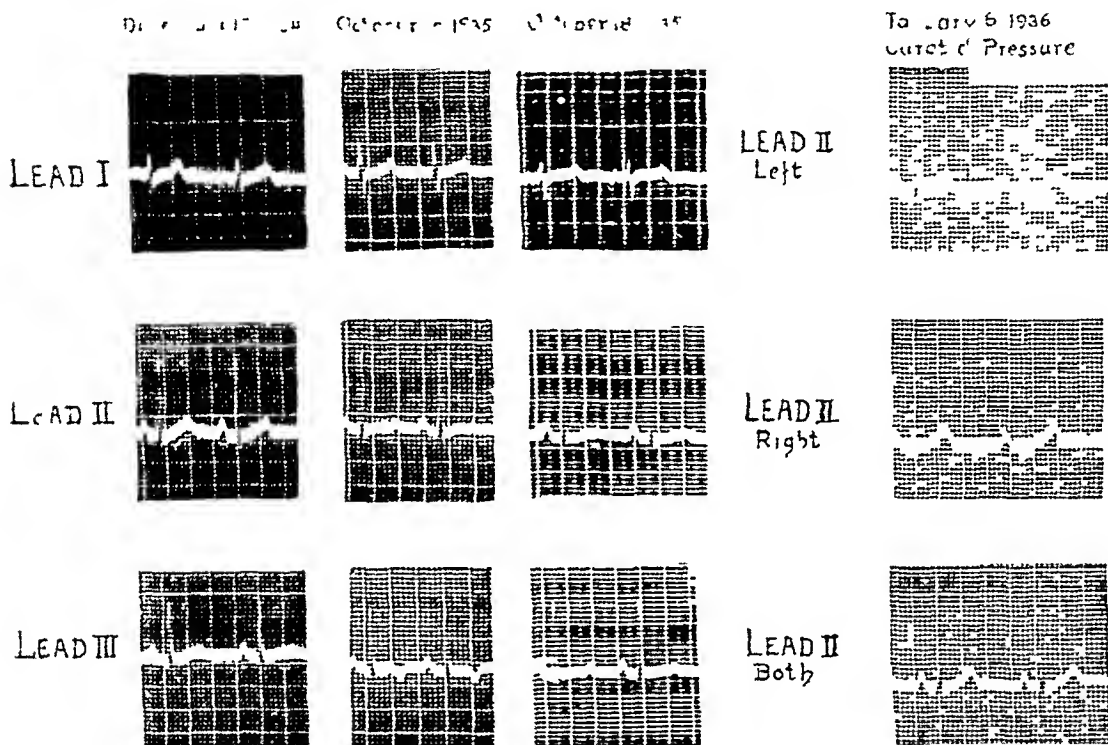


FIG 6 Transient changes in T-waves particularly in Lead II unassociated with any clinical evidence of disease

Physical examination at that time showed no evidence of disease. The heart was not enlarged, the rhythm and sounds were normal, with a rate of 72 at rest. There were no murmurs. The blood pressure was 120 systolic and 65 diastolic. The response of the heart rate and the blood pressure to exercise was normal. A seven foot plate of the chest showed the heart normal in size and shape, and the aorta normal in appearance. Electrocardiogram showed normal mechanism, rate 98. The auriculo-ventricular and intra-ventricular conduction times were within normal limits and all T-waves were upright and of normal shape.

A diagnosis of irritable heart was made and he was allowed to resume strenuous activity—to include football playing. He was seen next in February 1935, five months later, at which time no mention was made of his heart, and physical examination was again negative.

In October 1935, one year after his first visit, he appeared because when warming up on the sidelines of a football game he would feel his heart pound and would be momentarily short of breath. In a few seconds these symptoms would pass, he would enter the game and play hard with no symptoms. He had had an unusually active preceding summer and avowed he never felt better.

Physical examination revealed a normal sized heart, rate 78, normal rhythm, no murmurs, blood pressure 120 systolic and 80 diastolic. The electrocardiogram, however, showed a definite change from that made one year previously (figure 6). The record now showed a peculiar diphasic character to the T-wave in Lead II and a considerable late inversion of the T-wave in Lead III.

This was very disconcerting. Because of our conviction that this boy had no myocardial or coronary disease as suggested by the electrocardiogram we sent him running up and down two flights of stairs. On his return to the laboratory there appeared a slight definite change toward normality. This tendency to change under observation, especially following a speeding up of the circulation confirmed us in our opinion that the electrocardiogram was recording only functional changes, and so he was again sent back to the football field. A check-up on January 6, 1936, after a strenuous athletic season, now showed a completely normal tracing. To test the effect of vagal stimulation on the mechanism, pressure was applied to the left, right, and to both carotid sinuses. No changes in the T-waves were produced by these measures, although the rate was definitely slowed.

The conclusions to be drawn from these experiences are that when isolated electrocardiographic abnormalities occur in the absence of any other signs of heart disease they must be viewed with skepticism. The functional nature of some of these may be demonstrated by appropriate measures such as by exercise, administration of atropine or deep breathing.

DISCUSSION

Such observations as the foregoing illustrate anew the dangers of interpreting an electrocardiogram without full knowledge of all the other clinical features of the case. The testimony furnished by the electrocardiogram can be properly evaluated only when all the evidence is in, or occasionally it will deceive us. It will always tell the truth but never the whole truth.

Now that this delicate instrument of precision is becoming an every day office accessory of the internist, it may be hoped that it will lose some of the aura of infallibility which hung about it in its laboratory days. It may then assume its rightful position, not as a court of last appeal in cardiac diagnosis, but as a very valuable adjunct to physical and roentgen-ray examinations.

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PUBLIC HEALTH CONTROL OF SYPHILIS *

By THOMAS PARRAN, JR , M D , Commissioner of Health, New York State,
Albany, N Y

As one after another of the epidemic diseases has declined or disappeared under the impact of public health effort, it is natural that the same technics should be directed against other major causes of sickness and death. Moreover the success of past and current public health measures has engendered the confidence of the tax-paying public which will support extension of community action into fields heretofore reserved to private effort.

These two facts make it inevitable that the public health control of syphilis should be the central problem now faced by health departments. In undertaking any public health measure, those of us responsible for securing and expending public funds must consider the extent of the hazard to health and life, the controllability of the disease, and the cost of effective control efforts.

EXTENT OF THE SYPHILIS PROBLEM

From the mass of conflicting statistics and statements about syphilis, it is difficult to sort out dependable facts. This is due both to the nature of the disease and the different methods of stating its extent. Syphilis often is a subclinical infection with an unrecognized onset. It has periods of latency, and the end-point or cure frequently cannot be determined. Both the past and the present true attack rates are still the subject of conjecture. Although it shortens the life span of its victims, the total effect on mortality is not known.

Moreover, in expressing the amount of syphilis in a community, one may refer to the number of clinically recognized cases which are under treatment at a given time, the attack rate of clinically recognized cases which occur in a specified period, or the findings from serological and clinical surveys among special groups. Since in every community an unknown number of cases are not diagnosed and treated, and since surveys of limited groups are made by serological tests of varying sensitivity, and since such groups are not representative in age, sex, and other respects of the whole population, none of these methods gives a complete picture.

Add to these inaccuracies the geographic, racial, sex, social, and age variation in syphilis prevalence, and the complexity of the problem becomes apparent. In fact, it probably is easier to eradicate syphilis in a population than to determine its exact prevalence and distribution. In spite of these inaccuracies and uncertainties, certain facts are clear and certain conclusions are warranted concerning the extent of the syphilis problem. These facts together indicate that the statement of Sir William Osler, that syphilis ranks

* Read at the Detroit meeting of the American College of Physicians, March 3, 1936

with tuberculosis and cancer as a major cause of death, is as true today as it was when he made it

In upstate New York a census of all cases under treatment by all physicians, hospitals, clinics and other institutions was made in 1927 and repeated in 1930 and 1935. In the last two surveys data were secured also as to the number of new cases which were diagnosed for the first time during the month of April

The total of cases under treatment *increased* from approximately 12,000 in 1927 to approximately 17,000 in 1935 (43 per cent), while cases of early syphilis *decreased* from 3,415 to 2,029 (43 per cent) during the same period

The total of cases diagnosed for the first time in April 1935 was 1,644 which, when compared with 1,899 diagnosed in a similar period in 1930, constitutes a decrease of 19 per cent. Early syphilis cases diagnosed for the first time in April 1935 were 462, as compared with the 1930 total of 854, a decrease of 46 per cent

The prevalence and attack rates in upstate New York as shown by our surveys are much lower than in southern states and in cities with large negro populations, but much higher than in certain mid-western rural areas

Studies by Nelson in Massachusetts show also a decline in new cases of the disease in recent years, but a continued increase in total cases

The decline in early cases in these two states from which recent reports are available suggests that at last the results of control efforts are apparent. The continued increase in the total of cases newly diagnosed impels caution, however, as to full acceptance as yet of this conclusion. A disturbing fact apparent from the data collected in this and other countries is the large proportion of late syphilis in the total of first diagnoses and clinic admissions. In Great Britain, for example, with accurate histories on admission for all clinic cases, more than one-half of the new admissions are cases of late syphilis. Case finding early in the disease leaves much to be desired

Although recent reports from Massachusetts and New York suggest a decrease in new cases of syphilis, the data available to the Public Health Service from the country as a whole do not indicate a decline. From Great Britain and the Scandinavian countries, on the contrary, reliable reports are available showing that syphilis in recent years has declined markedly, and in the Scandinavian countries the disease now shows only a small fraction of its former prevalence. With frank skepticism, I undertook a study last summer of their data, their methods, and results. Three critical colleagues confirm my statement that the Scandinavian reports are genuine. Syphilis there has become a rare disease. In Sweden, with a population of 6,100,000 (almost the same as upstate New York), there were just 431 cases of the disease in 1934, in the first half of 1935 there were only 200 cases. Multiply the population and cases by 20 and the data are comparable with those for the United States. If the rate for Sweden were applied to the whole population of the United States, we would have annually only 8,620 cases. Compare this with the Public Health Service estimates of 420,000. The

rate in Sweden now is only one-tenth of the rate 15 years ago. That inadequate reporting is not a factor is confirmed by the continued high prevalence of gonorrhea, amounting to approximately 12,000 new cases in 1934. This fact, too, makes it clear that medical measures rather than moral restraints have brought about the decline in syphilis.

In Denmark an almost comparable decline has been recorded. In that country all Wassermann tests for the whole country are done in the one State Serum Institute, where complete records have been kept of every examination, positive and negative, during the past 16 years. Denmark has a population of 2,600,000. In 1933 syphilis cases totalled 648. At the peak of the post-war epidemic in 1919 there were 7,024 cases. In Copenhagen the decline has been even greater—from 2,189 to 181. Here, too, the prevalence of gonorrhea has continued high.

In Norway, data for the country outside of the capital, Oslo, are incomplete. In this city, however, the cases per 100,000 population decreased from 360 in 1919 to 30 in 1935.

In Great Britain, where there is no reporting of cases but where a large percentage of the total is treated in public clinics, new admissions have declined by more than one-half since 1920. The 20,692 new admissions to clinics in Great Britain and Wales in 1934 represent an admission rate of 54.3 per 100,000 population. This should be compared with the upstate New York clinic admission rate of 112.6 for the same period.

While the methods in these countries differ in many respects, the provision of public clinic facilities of a good quality, available to all patients, is the factor common to each. In addition, the Scandinavian countries require notification of cases, and treatment is compulsory. In Sweden the careful investigation made of sources of infection is a noteworthy feature.

CONTROLLABILITY OF SYPHILIS

It is not surprising that countries which have undertaken systematic control measures have gotten results, since the facts concerning syphilis argue for its controllability. The causative agent is known, a diagnosis can be made as soon as the case is infectious, we have serological tests which will discover otherwise latent cases, in the arsphenamines, we have remedies which will speedily sterilize the infectious case. Unlike such diseases as typhoid fever, syphilis is spread singly from person to person by intimate contact. The source of infection and those exposed usually are known to the patient.

Compare these facts with tuberculosis, a disease which has declined by two-thirds during the past 30 years. For tuberculosis, there is no specific method of cure or of rendering the patient non-infectious. Diagnosis of the early case is costly and difficult. The infectious agent is widely disseminated in the population. In spite of these greater difficulties, the practical control and even eradication of tuberculosis in this country is a goal.

clearly in sight. The great difference between these diseases, however, is that, in the case of tuberculosis, we have promoted public knowledge of the disease, mobilized the profession, created public facilities, and organized community programs of control.

In spite of knowledge concerning syphilis, which seems adequate for control, we must not lose sight of certain biologic facts which make the problem difficult: the obscure nature and transitory character of the initial lesion, the tendency of the disease to relapse under inadequate treatment, the possibility of second and completely blind infections, the unknown rôle of the chronic carrier as a factor in spread, and the possible reversion of the organism to a more virulent form. These factors are important and need further study. Since our present methods do not appear to have brought about a decline in syphilis prevalence, it is fair to ask if we have neglected to use to best advantage all available weapons.

EPIDEMIOLOGICAL APPROACH

During recent years, the studies of Munson in New York and of Smith and Brumfield in Virginia demonstrate clearly that, by the use of the epidemiological method, undiscovered sources of infection can be found and brought under treatment. Evidence has accumulated also which shows that syphilis does not spread evenly in the population, but that it is kept alive and spreads chiefly by a series of small epidemics. Munson traced more than 30 such local outbreaks, averaging four or five cases each, most of which were not under treatment. Smith and Brumfield have shown that from 157 new cases of early syphilis 345 contacts or potential sources were named (representing 278 persons), of whom nearly one-half were located and brought under treatment. Of these cases, all were in the early infectious stage of the disease and had not been under treatment previously. These methods have been tried in New York State in recent years with results sufficiently gratifying to warrant the state-wide application of the principle. In the epidemiological method, we have an unused instrument for the control of syphilis which, in my opinion, is of as much value as the Wassermann test or the arsphenamines.

NEW YORK PROGRAM

Before starting our program, it was discussed with the Public Health Committee of the State Medical Society, and many details worked out with the advice of its members. As finally agreed upon, it was approved by this committee and the Executive Committee of the State Society.

Our syphilis control program has four major objectives: (1) The notification of cases, (2) intensive and complete investigation and supervision of sources of infection, cases and contacts, (3) the provision of facilities for adequate diagnosis and treatment, (4) professional and public education.

In New York City essentially the same plans are being developed but modified to fit the particular needs of that large metropolis

For administrative purposes, the State (outside of New York City) is divided into 33 districts comprising the 12 cities of more than 50,000 population, the five county departments of health and 16 state health districts. The program is carried out by the city and county departments of health with state-aid if State standards are met. Outside of the large cities and the five counties with departments of health, state-aid is given to local clinics, but reports are made directly to the state district office, and state personnel is used for the epidemiological work.

CASE REPORTING

The starting point is a state-wide system of approved laboratories. Whenever a physician diagnoses or suspects the existence of syphilis or of another communicable disease, an appropriate specimen must be sent to an approved laboratory accompanied by information as to whether the specimen is for diagnosis or treatment control, the stage of the disease, and other pertinent facts. The laboratories are required to submit copies of all positive reports to the local health officer or the state district officer. Physicians are required to make a case report of each case of syphilis, giving sex, date of birth, and address, but it is not necessary for the name to be given. Thus the identity of the cooperative private patient is safeguarded. These reports are checked against the positive laboratory findings to insure completeness.

Physicians are required, however, to report by name any lapsed infectious case, and health department nurses are available to follow up such lapsed cases and return them to their physician for further treatment. Another service is the furnishing of free arsphenamines and bismuth to private physicians for private patients, as well as to clinics.

When a case of smallpox seeks treatment, the first impulse of any good physician is to call the health officer. Is it too much to hope that we can create the same interest in the source of early syphilis? Is it unreasonable to ask that an obligation to the community no less than to the patient be assumed in this as in other infectious diseases?

All cases of syphilis are classified into three categories: (a) early syphilis (less than one year since onset), (b) other potentially infectious cases, (c) late non-infectious cases. The term "potentially infectious" is applied to the following types of cases regardless of the presence or absence of visible lesions:

- 1 All patients with acquired syphilis who have received less than 20 injections each of an arsphenamine and a heavy metal, or equivalent treatment, until five years have elapsed since onset.

- 2 All female patients with acquired syphilis inadequately treated, until the menopause has been reached.

3 All patients with early congenital syphilis

Efforts to determine sources of infection are limited to early syphilis. Investigation of contacts, however, and supervision of cases are extended to include also all potentially infectious cases, but with major emphasis on persons 15 to 30 years of age and cases of less than 2 years' duration.

EPIDEMIOLOGICAL WORK

In each of our 33 districts a trained medical officer with one or more nurses and sufficient clerical assistance is responsible for the syphilis epidemiological work. When a physician reports a case in private practice, the medical officer goes or telephones to the physician himself and asks him either to permit the health department to investigate the case or to make this investigation himself in order to locate, if possible, the source of infection. If the physician elects to assume the responsibility, he again is given the choice of getting the source of infection and contacts under treatment, or permitting the health department to do it. After six months' trial in our larger cities, I am happy to report that in practically no instance have the physicians failed to cooperate. It is beginning to be apparent, however, that the record of the private physician in ascertaining sources of infection is not as good as that of the trained epidemiologist. An epidemiological record card is executed for each early case, which is comparable in completeness to the records used in the investigation of typhoid fever, for example.

No investigation of an early case is acceptable unless the source of infection is found, or unless satisfactory evidence is submitted to establish beyond reasonable doubt that this individual cannot be identified and located. Results to date indicate that, in from 20 to 30 per cent of all cases of early syphilis, the source of infection can be located and brought under treatment.

APPROVED CLINICS

An essential part of our program is to elevate the quality of clinic service. Those clinics which meet prescribed standards are designated as "approved clinics"*. Until recently most physicians have served in syphilis clinics without compensation. Provision now is made for paying all such physicians. The rate of payment varies, but averages about \$10 per session.

The following classes of patients are eligible for treatment at clinics irrespective of whether or not they are residents: (a) any patient for initial diagnosis and emergency treatment if found to be infectious, (b) any patient

* Standards for "approved clinics" may be summarized as follows. They must be conveniently located with adequate quarters and separate waiting rooms or separate sessions for men and women. Records containing prescribed minimum information must be kept. The treatment of early syphilis must be a continuous system and in conformity with modern accepted practice. Spinal fluid examinations must be performed whenever possible before the patient is ready for discharge. In the larger centers facilities for cardiovascular and other examinations must be provided. Each clinic must have adequate medical, nursing and clerical personnel. In each city daily clinic service must be provided with at least one evening session per week, and facilities must be provided to determine the financial status of patients.

unable to pay a private physician for treatment, (c) any patient referred by physician for consultation, such case to be returned to the referring physician with examination reports and advice for further treatment. The acceptance of non-resident patients and the introduction of consultation for the general practitioner as a function of the clinic are new features.

Definite requirements are made concerning the reporting of cases which lapse for more than one week, and an automatic procedure of follow-up is established. Wherever possible, improvement of existing clinics attached to hospitals is sought, rather than the setting up of separate clinics.

There are approximately 120 syphilis clinics in upstate New York, and we are now engaged in studying these clinics and specifying the changes necessary to qualify for approval and state aid.

In the centers of population too small to support a clinic service, the local health officer is required by law to provide treatment of any person with a venereal disease unable to pay a private physician. For this service he is entitled to payment at rates comparable to those paid for other public medical services.

EDUCATION

Major emphasis thus far has been put upon professional education. This includes the training of physicians and nurses in the public health and clinical aspects of the problem.

An extension course in social hygiene was given to more than 1 000 public health nurses two years ago. This was followed last year by a summer course at Syracuse University for 70 nurses selected for this special work in clinics and health departments. Another such course will be held this summer for a larger group. In addition, we are assembling a corps of young physicians and giving them special training in public health and in the epidemiological method of syphilis control. A number of the leading syphilologists in the State are assisting us on a part-time basis as consultants in promoting the organization and quality of clinic service, and in professional education.

A series of regional institutes will be held this year primarily for clinic physicians. Attendance is promoted by compensating these physicians for time lost from practice. These institutes will be open to other interested medical men. Moreover, a number of County Medical Societies are holding for practitioners postgraduate courses in syphilis therapy. By these several methods we hope to compete with the pharmaceutical "detail men" in teaching the general practitioner how to treat syphilis.

For several years we have had the active cooperation of the State Committee on Tuberculosis and Public Health in promoting public interest and knowledge of syphilis. Some progress has been made in breaking down the barrier of public ignorance and apathy. Our Governor and Legislature have been willing to provide funds. They have been convinced that the cost of a syphilis control program is less than the cost of continued neglect. The

newspapers, and recently the National Broadcasting Company have permitted the word syphilis to be used. Health departments and physicians must seize the opportunity and be prepared to furnish needed information. Yes, the word *syphilis* must be spoken, heard, printed, understood.

SUMMARY

The prevalence of syphilis in the United States continues to be high, and its control is the most urgent public health task with which health authorities are confronted.

The Scandinavian countries, and Sweden in particular, by organized national effort have accomplished a modern miracle in medicine—the practical eradication of syphilis.

The epidemiological method of locating infectious sources is an unused weapon, but potentially as valuable as the arsphenamines and serodiagnosis.

New York State is undertaking a serious state-wide control program with full cooperation of the medical profession.

What the health department is doing in New York can and should be done in every State. Available Federal funds for Social Security make it possible.

In the public health control of syphilis, the members of the American College of Physicians have an opportunity this year, each in his own community, to sponsor and support a great work for a high purpose, with assurance of good results to the public.

THE CLINICAL ASPECTS OF AMYLOIDOSIS¹

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INTRODUCTION

FROM the nosological aspect generalized amyloidosis has not received its due recognition. It has hitherto been largely viewed as an ominous sequel of chronic suppuration, with cachexia, anemia, swelling of the liver and spleen, and albuminuria as the most prominent clinical expressions. In recent years, new data have been established which have widened the diagnostic basis of this disease. These are the recognition (1) of primary amyloidosis, (2) of so-called atypical amyloidosis, (3) of the relation of general amyloidosis to "nephrotic," or better termed, hypoproteinemic states, and (4) the establishment of the Bennhold Congo red test. These viewpoints and the opportunity to observe a considerable number of cases of amyloidosis, both primary and of unusual etiology, have stimulated this study.

A MORBID ANATOMY

The amyloid substance is deposited in the mesenchyme and more particularly in the reticular and collagenous tissues of the periglandular and pericapillary structures. The reticulo-endothelial system is usually profoundly affected. Epithelial tissues are comparatively free from amyloid invasion. Friedreich and Kekulé¹ first showed that the amyloid substance was protein in nature. For a long time, amyloid was supposed to be a compound of protein with chondroitin-sulphuric acid, but Hanssen² who studied amyloid in pure form found no chondroitin-sulphuric acid. Eppinger³ in his chemical analysis of a solitary amyloid mass, found within a liver, determined that the dried material contained purines, diamine acids and much tyrosine. There was no carbohydrate, phosphorus or sulphur. Apparently amyloid is not always uniform in chemical composition, because in some of the atypical forms of amyloidosis the staining reactions are bizarre (Lubarsch⁴).

The organs most frequently involved in generalized amyloidosis are, in the order of frequency, the spleen, liver, kidney, suprarenals, and lymph nodes. This incidence corresponds to that found in experimental amyloidosis (Jaffe⁵) and to that found in horses used in antitoxin production (Doerken⁶). Less frequently amyloid is deposited in the intestines and pancreas. Lubarsch never saw amyloid in the brain. In the atypical form of amyloidosis amyloid has been found in almost every organ of the body: the tongue (Pick⁷), the bone marrow (Gerber⁸), the skin (Konigstein⁹),

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From the Service of Dr. B. S. Oppenheimer, Mt. Sinai Hospital, New York City

the muscles (Warren¹⁰), the heart (Budd¹¹), and in tumors (Weber,¹² Glaus,¹³ Hueter¹⁴)

The detection of amyloid in tissues is entirely colorimetric, and depends upon the histological reaction of this substance to the methyl violet stain and to iodine

Etiology That amyloidosis follows chronic suppuration is well known. Of 112 autopsies in Montefiore Hospital in which amyloid was present, Rosenblatt¹⁵ found that in 100 there was an associated tuberculosis. This represented 25 per cent of all patients dying with this disease. Of the remaining 12, three had no apparent cause, two were associated with carcinoma of the lung and secondary suppuration, one was associated with a chronic osteomyelitis, three with pyelonephritis, one with carcinoma of the stomach, one with leukemia and one with tabes dorsalis. Of 100 cases of amyloid disease involving the kidney, reported from the Philadelphia General Hospital by Dixon,¹⁶ 78 per cent were associated with tuberculosis of the lungs or bones, 9 per cent with malignant tumors, 5 per cent with empyema, 2 per cent with chronic arthritis, 2 per cent with osteomyelitis, 1 per cent with bronchiectasis, 1 per cent with lung abscess, and in 3 per cent the cause was unknown.

At Mt Sinai Hospital, amyloid change was found in 42 autopsies from the year 1916 to the present. Of these, 11 were caused by tuberculosis of the lungs, 10 by lung abscess or chronic bronchiectasis, three by chronic osteomyelitis, four by neoplasms, two by Hodgkin's disease and one each by subacute bacterial endocarditis, lues of the aorta and liver, chronic ulcerative colitis, tuberculous osteomyelitis, tuberculous pyonephrosis, tuberculous entero-colitis, perinephritic abscess, general tuberculosis, tuberculous coxitis. Two cases were primary. Of the total, 16 were caused by tuberculosis. This report does not include clinical cases of amyloidosis observed at Mt Sinai Hospital during this time, but it represents a valid cross section of the incidence in relation to etiology.

There is an interesting association between amyloid and myeloma. Magnus-Levy¹⁷ in 1931 collected 19 such cases. The amyloidosis may be generalized but more often it is localized in unusual sites, such as the muscles, the dura mater, the abdominal wall, the intestines, the bones, tongue, esophagus, etc. Magnus-Levy regards the amyloid substance and Bence-Jones protein as chemically related. He found small quantities of Bence-Jones protein in myeloma tissue especially in crystalline form. He does not believe that the Bence-Jones protein is transported. He also found Bence-Jones protein in the body fluids, in the blood serum, in serous effusions and in the bone marrow, and only rarely in the liver, spleen and kidneys. The reason it is found only in small quantities in these fluids is, he believes, because it is rapidly formed and excreted. Bell¹⁸ reports a case of amyloid with myeloma in which the extensive amyloid infiltration of the muscular wall of the intestine caused obstruction.

The association of generalized amyloidosis with malignant blastomata is not uncommon. Usually the tumor shows extensive necrosis. Lubarsch saw amyloid 20 times in a series of 398 cancers, and in a large percentage of experimental mouse cancers. We are not referring here to the cases of localized microscopic or extensive amyloid infiltration of blastomata, usually myeloma, that have been reported (Weber, Glaus, Hueter).

The occasional association of amyloidosis with non-suppurative maladies is not always to be regarded as cause and effect. For instance, the simultaneous occurrence of chronic deforming arthritis and amyloidosis is reported too infrequently (Dixon, Rosenblatt, Perla and Gross¹⁹) (cases 1 and 2 in my series may be included) to be more than an accidental association. In all likelihood, the arthritis is not the cause of the amyloidosis, rather both conditions are simultaneous reactions to the same insult.

Primary amyloidosis forms a not inconsiderable section of all reported cases, especially of the localized or atypical variety, and offers a difficult problem for diagnosis. Such primary cases comprise a distinct nosological entity which requires serious consideration.

CASE REPORTS

Case 1 S. H., aged 57, was admitted to the service of Dr. B. S. Oppenheimer, September 14, 1934. The previous history was irrelevant. Four years ago, following the onset of menopause, the patient developed pain, swelling and stiffness of the joints, many of the joints showed an effusion. Subsequently the joints of the hands and feet became deformed. During the past three years there has been swelling of the lower extremities and increasing loss of weight. Five weeks previous to hospitalization she developed anorexia, nausea and vomiting and she also noted that her skin was becoming dark. On examination, in addition to the pigmentation of the skin, there was a bilateral conduction auditory defect, yellowish exudates in the right fundus, a heart enlarged to the left with sounds of poor quality, a systolic murmur was heard over the precordium but loudest at the base, the blood pressure was 110 systolic and 60 diastolic. The peripheral vessels were not sclerosed. The liver was enlarged, reaching 3 cm. below the costal margin. The muscles of both hands were atrophic, there was ulnar deviation, spindle shaped fingers and swelling of the metacarpal joints. The knee joints were red, swollen and tender. There was tenderness of both shoulder joints, and slight edema of both lower extremities. The hemoglobin was 60 per cent, red blood cells 3,400,000, white blood cells 8,000, polymorphonuclears 50 per cent. The urine showed a specific gravity of 1.014 after the concentration test, there was a heavy precipitate of albumin on boiling and casts were present. The blood cholesterol was 290 mg. The urea 27 mg. The total blood protein was 6.2 per cent, of which the albumin fraction was 2.3 per cent and the globulin 3.9 per cent. The Congo red test showed 70 per cent tissue retention. A diagnosis of primary amyloidosis was made. Liver extract was given intramuscularly and by mouth. For a while there was some general improvement. An examination one year later revealed no appreciable change from her previous condition.

Summary A woman of 57 with a history of deforming general arthritis of four years' duration, the onset of which was followed shortly by symptoms of the so-called nephrotic syndrome with anemia and weakness and simultaneous enlargement of the liver and spleen. The Bennhold Congo red test confirmed the clinical impression that the case was one of generalized amyloidosis. No cause was discoverable. One year later the condition of the patient was unchanged.

Apparently the association of amyloidosis with chronic arthritis is not as rare as generally regarded. The following instance shows that it may occur even in early childhood.

Case 2 A child, aged $2\frac{1}{2}$ years, was admitted to the service of Dr. B. Schick on April 18, 1933 and discharged January 2, 1935. She had suffered with convulsions since the age of one. Shortly after the last convulsion pain in the left thigh and knee appeared followed by pain in the left elbow. Fever appeared two weeks before admission.

On admission she had a temperature of 101.6° F. There were stiffness and tenderness of the lower cervical spine. The left wrist was swollen, hot and tender. The left ankle was swollen and tender. The liver and spleen were not palpable. A soft systolic murmur was heard in the fourth interspace, not transmitted. The urine was normal. The hemoglobin was 61 per cent, red blood cells 3,900,000, white blood count 18,800 with a normal differential count. The sedimentation rate was 31 minutes. The electrocardiogram showed sinus tachycardia. Roentgen-rays of the joints showed no pathologic changes.

For the next nine months the child ran a febrile course, then she became afebrile. The fever reached 104° and she had occasional chills. Blood cultures on several occasions proved sterile. There was progressive loss of weight. Roentgen-rays of her knees taken four months after admission showed marked swelling of the soft tissues with some periosteal thickening of the upper end of the right ulna. A roentgenogram of the chest showed nothing abnormal. The use of typhoid vaccine and removal of the tonsils had no effect upon the progress of the disease. About nine months after admission the liver became palpable two fingers' breadth below the costal border. The urine contained large amounts of albumin. A Congo red test showed 50 per cent retention at the end of one hour. There was 65 per cent excretion of phenolsulphonephthalein at the end of two hours. The concentration of urine was normal. The sedimentation time varied between 5 and 15 minutes. A Congo red test done eight months after admission showed 100 per cent retention. Roentgen-rays about this time showed marked atrophy of all the bones in both knees. The epiphyses were large and irregular, and there was considerable calcified material between the epiphyses. Wassermann tests were negative.

Case 3 C. B., a woman, aged 56 years, was admitted to the hospital (to Dr. B. S. Oppenheimer's service) January 28, 1934. One year previous to her admission she had noted red blotches on the right side of her neck. These lesions were evanescent. However, during the last six months the blotches appeared more frequently, became more extensive, and spread to the left side of the neck, lower eyelids and trunk. They were dark red and irregular in shape. During the past two years she had noticed blood on her handkerchief on blowing her nose. About three months ago while eating she noticed a blue blister beneath her tongue which burst and bled for half an hour. She estimated the quantity of blood lost as about a cupful. There was marked anorexia, and the patient had lost 11 pounds in the four month period previous to admission. She had experienced attacks of precordial oppression and dyspnea on exertion. Palpitation was severe and frequent. She had had numbness of the fingers for the past two years, and for six months sensations of pins and needles in her fingers.

Examination showed a thin, gray-haired woman with cyanosis of the lips. There were arteriosclerotic changes in the vessels of the fundi. The uvula was swollen and ecchymotic, and there were numerous groups of large petechiae on the buccal mucosa, some of which had white centers. The chest was emphysematous and the dorsal spine kyphotic. The lungs were clear. The heart was normal except for frequent extrasystoles. The blood pressure was 140 systolic and 80 diastolic. The liver was

palpable to the umbilicus, and was unusually hard and firm. The spleen was enlarged to three fingers below the free costal border. On the left side of the neck, on the eyelids, and in the right groin there were large purpuric spots. There was no lymphadenopathy.

The hemoglobin was 80 per cent, red blood cells 5,000,000, platelets 230,000, white blood cells 12,000, polymorphonuclear neutrophils, 44 per cent, lymphocytes 54 per cent, monocytes 1 per cent and eosinophils 1 per cent. The tourniquet test was negative. The brom-sulphthalein and galactose tolerance tests gave normal results. The urine on repeated examinations contained abundant albumin, a few white blood cells, hyaline casts, and on one occasion an amyloid cast. There was no Bence-Jones protein in the urine. Roentgenologic studies of the gastrointestinal tract failed to reveal any lesion. Roentgenograms of the chest showed only a hypertrophy of the left ventricle. Roentgenograms of the bones revealed no lesion. A Congo red test showed 100 per cent tissue absorption at the end of one hour. In view of the fact that no other cause for the symptoms was ascertainable, the diagnosis of primary generalized amyloidosis was made. While in the hospital she had repeated crops of cutaneous hemorrhages. On one occasion she had frank blood in the stool, and sigmoidoscopy revealed numerous petechial hemorrhages in the rectal and sigmoidal mucosa. The blood fibrinogen was 350 mg. The blood protein was 7.8 per cent, of which 4 per cent was albumin and 3.8 per cent globulin. The cholesterol was between 340 and 375. The Van den Bergh reactions were normal. The blood Wassermann test was negative. The sedimentation time was 23 minutes.

She was given liver extract intramuscularly, 2 c.c. twice a week. The patient left the hospital on March 7, 1934 and died three weeks later. Her private physician's diagnosis of the cause of death was "uremia."

Summary A woman, aged 56 years, showed purpuric lesions of the skin and mucous membranes for one year. The liver and the spleen were considerably enlarged, there was marked albuminuria, a normal blood pressure, a normal blood protein with an elevated blood cholesterol. The diagnosis of amyloidosis was made and confirmed by the Congo red reaction which showed 100 per cent absorption.

Case 4 L. C., male, aged 38, admitted to the service of the late Dr. N. E. Brill, September 25, 1923. The family history was irrelevant. Twenty years before he had had a chancre and four years before a left-sided "pleurisy" which lasted two weeks. For 10 years he had had occasional frontal headaches. Five years prior to admission he noted dyspnea on exertion. This gradually increased and recently he had suffered from precordial pain when he hurried. About two months before admission his feet began to swell. For the past week he had had choking sensation, dyspnea and swelling of the abdomen. His ears had begun to discharge two months before entry to the hospital.

On examination he presented a diffuse anasarca with edema of the feet, hydrothorax and ascites. The heart was somewhat enlarged, with a short systolic murmur at the apex. The blood pressure was 160 systolic and 50 diastolic. The blood showed a moderate secondary anemia. The temperature was 100.2° F. and the pulse varied between 92 and 120. The knee jerks were absent. The urine contained abundant albumin and many hyaline casts. The blood urea nitrogen was 14 mg. per 100 c.c., cholesterol 170 mg., glucose 200 mg., and carbon dioxide 46.2 volumes per cent. The blood Wassermann test was negative. He died the day following admission in pulmonary edema.

Autopsy The tracheo-bronchial lymph nodes were anthracotic. Both pleural sacs contained one liter clear fluid. The lungs showed edema and passive congestion. The pericardial cavity contained 100 c.c. of clear fluid. The musculature of the heart was dark brown and showed marked fatty changes. The mitral valve was thickened. The coronary arteries showed slight arteriosclerosis. The aorta showed a

few arteriosclerotic plaques in the arch and in the sinuses of Valsalva. The abdomen contained 1.5 liters of clear fluid. The liver was congested and fatty. The spleen was enlarged, deep red and showed an increase in fibrous tissue. The adrenals were normal. The pancreas was fibrotic. The kidneys were large, the capsules stripped easily and the cut surface was smooth and brown. The glomeruli were hardly visible. The microscopic examination showed passive congestion of the lung and liver, and diffuse amyloid change in the liver, spleen, kidneys and adrenals.

It seems rather strange in view of the frequency of chronic ulcerative colitis that amyloidosis has hitherto not been reported as a sequence, as in the following case.

Case 5 F P, aged 48, was admitted to the service of Dr B S Oppenheimer November 7, 1931 and died January 17, 1932. She gave a history of three operations for rectal stricture. Three months before admission her legs and abdomen began to swell.

The patient was emaciated and presented a large liver, a purulent discharge from the rectum and edema of the back and legs. The blood pressure was 134 systolic and 80 diastolic. The hemoglobin was 48 per cent, red blood cells 2,650,000, white blood cells 2,600, of which 77 per cent were polymorphonuclears. The urine contained large amounts of albumin. The stools gave a strongly positive test with guaiac. The Congo red test showed a retention of 29 per cent. The blood urea was 14 mg, the blood glucose 75 mg, the cholesterol 165 mg per 100 cc. The blood Wassermann test was negative. The blood serum proteins were 4.6 gm of which the albumin fraction was 2 and the globulin 2.6 gm. Sigmoidoscopy revealed a granulomatous mass involving the lower rectum and the anus, the posterior vaginal wall was also involved. The remainder of the gastrointestinal tract was normal by roentgen-ray. The chest was normal. A barium enema revealed marked constriction of the mid-sigmoid with fistulous communication between the sigmoid and ileum. A colostomy was performed but the patient continued to fail and she died a short while thereafter.

Anatomical diagnosis Chronic ulcerative stenosing proctitis with multiple fistulae, chronic sigmoiditis and colitis (descending colon), chronic cystitis, terminal ileitis. Amyloidosis of the kidneys. Dilatation of the right auricle and ventricle, broncho-pneumonia of the left upper lobe. Thrombosis of the left pulmonary artery, chronic infectious swelling of the spleen. Pyelonephritis. Hydrothorax. Perihepatitis and perisplenitis. Organizing emboli of left pulmonary artery, pulmonary infarct.

Summary A woman of 48, with a long standing chronic colitis and terminal ileitis with multiple intestinal fistulae, who developed a nephrotic syndrome caused by renal amyloidosis. The Congo red test showed a retention of the dye within the normal range, proving that the test is not infallible. The amyloidosis was limited to the kidney.

Case 6 A woman, aged 23, admitted to the service of Dr G Baehr, had an ileostomy performed seven years before for ulcerative colitis. Following this she was readmitted to the hospital on several occasions, once for intestinal obstruction with nausea and vomiting which subsided within several days and once with an ischio-rectal abscess which was incised and drained and which continued to drain up to the time of admission. She had also developed a recto-vaginal fistula and a peri-rectal abscess. The ileostomy functioned well and she was able to carry on a somewhat restricted life. One year before this admission she vomited about once a month. The vomiting was accompanied by mild abdominal discomfort and was not profuse. Her last bout of vomiting occurred two weeks before admission. Nine days before admission she noted oliguria and two days later complete anuria. At that time she began to vomit profusely and continued to vomit until the time of admission. Head-

aches and dizziness accompanied this spell of vomiting. Physical examination showed a poorly developed, poorly nourished female, appearing acutely ill. The breath was uriferous. The heart sounds were of fair quality. The blood pressure was 90 systolic and 70 diastolic. An ileostomy of the right lower quadrant, apparently functioning well, was present. There was an anal stricture not admitting the examining finger. There were discharging granulating ulcerations of the right inguinal and right ischio-rectal regions. The extremities were cold and clammy. There was a positive Chvostek sign. The hemoglobin was 36 per cent, red blood cells 2,100,000, white blood cells 7,200. Her urine showed abundant albumin and innumerable casts. The urea nitrogen on admission was 178 mg, calcium 63 mg, phosphorus 77 mg, chlorides 350 mg per 100 c c. The CO_2 49.5 volumes per cent. The electrocardiogram showed sinus tachycardia with tendency to left ventricular preponderance. The sedimentation time was 7 minutes. The phenolsulphonephthalein test showed no excretion. Scrapings from the fistulae showed no evidence of tuberculosis. The fundi were normal. The von Pirquet test was negative. The Mantoux test was positive with a 1/1000 dilution. A concentration test of the urine showed a maximum concentration of 1012. The patient was given intravenous glucose and saline solution, and calcium gluconate. Her urinary output gradually increased, signs of tetany subsided, the blood urea gradually fell to 70 mg per 100 c c. Her blood chlorides rose to 550 mg, calcium rose to 104 mg, phosphorus fell to 43 mg, the total protein was 63 per cent, albumin 23 per cent, globulin 31 per cent. Her urine, however, continued to show abundant albumin with occasional hyalin and granular casts and many leukocytes. Her blood pressure ranged from 64 systolic and 48 diastolic to 86 systolic and 46 diastolic.

The Congo red test showed 100 per cent retention on one occasion and 95 per cent retention on another occasion. In retrospect the clinical picture was explained on the basis of a long standing chronic oliguria with associated nitrogen retention producing vomiting from time to time and finally reaching such a stage that vomiting became continuous with resulting anuria. A vicious cycle by loss of chlorides caused an extreme azotemia with peripheral collapse.

Whether or not an intercurrent glomerulonephritis was present is merely conjectural. The urine was free of lead and arsenic. The patient was given liver extract and a transfusion. There was a moderate improvement in her general condition, and she was discharged from the hospital one month after admission.

THE MECHANISM INVOLVED IN THE PRODUCTION OF AMYLOIDOSIS

Experimental Amyloidosis In what manner do suppuration and tissue necrosis bring about the production of amyloid substance in the mesenchyme? Some light has been thrown upon the problem by the successful experimental production of amyloid. Credit for the first valid experimental production of amyloidosis belongs to Kuczynski²⁰ who in 1922 produced amyloid disease by the injection of 5 per cent sodium caseinate over prolonged periods into mice, he also found that it could be produced by excessive feeding of such protein. Since then Kuczynski's work has been repeatedly confirmed, especially by Smetana,²¹ Jaffe,²² Lucke, Letterer,²³ and Grayzel, Jacoby and Warshall²⁴. Jaffe carried on his work on an extensive scale. He employed a 3 per cent solution of sodium caseinate in normal sodium chloride solution injected into mice every few days. After the sixtieth injection the results were uniform, so that he could always find amyloid in the spleen. After the eightieth injection the amyloid was

distributed in most of the parenchymatous organs, i.e. the spleen, the liver, the kidneys, suprarenal glands, the lymph glands and the intestines. Eventually every organ was affected except the skin and the central nervous system. He obtained the same results by the repeated injections of sterile human serum so that he regards amyloidosis as due to chronic protein poisoning. Jaffé and others have found a crystalline form of amyloid in experimental animals which apparently is only rarely found in human amyloidosis. He found that the blood of his experimental animals showed a normal refractometer index and a normal hydrogen-ion concentration.

Grayzel, Jacoby and Warshall found that diet influenced the production of amyloidosis. An adequate diet but one containing an abundance of vitamins A and B will retard the development of experimental amyloidosis. They also noted the resorption of amyloid in animals in the early stages if powdered whole liver was added to the diet. No resorption was noted in the advanced stages. It is upon these observations that the treatment of amyloidosis by liver is based.

Letterer produced amyloid not only with sodium caseinate, but with gelatine, egg albumin, cereal albumin, nuclein and peptone. He also implanted portions of normal spleen and kidneys and occasionally obtained amyloidosis. Occasionally he produced amyloid with injections of selenium, especially if the animals were fed little water. The ingestion of water seemed to have an influence on the production of amyloid even with sodium caseinate injections, water restricted animals required a much smaller dose than those who were given water freely.

In this connection, the findings of Doerken and Arndt²⁵ are pertinent. They studied the incidence and histological reactions of amyloid in 100 horses employed in the production of antitoxin. They found that 60 per cent of these animals showed amyloidosis, and the incidence of affection of the various organs parallels closely those observed in human and experimental amyloidosis. The animals had been used for the production of different varieties of antisera for two and a half to 54 months. Before the eighth month, amyloidosis was never found, after the sixteenth month nearly always and after the twenty-first month always. Curiously, the horses employed for the production of scarlet fever antisera showed a greater incidence of amyloidosis than those used for productions of tetanus or diphtheria antitoxins. Unfortunately no observations upon the total protein content of the blood of these horses were made, but it is interesting to note, as upholding Letterer's contention, that hyperglobulinemia is the direct cause of amyloidosis, that Reitstotter²⁶ found in serum treated horses an increase of globulin, sometimes up to 100 per cent at the expense of the albumin fraction.

The changes noted by many observers in the blood protein when protein is added to the body economy either parenterally or otherwise are significant. Moll²⁷ found an increase of globulins in the blood after repeated injections of protein gelatin and killed bacteria. Rowe²⁸ found an increase in blood

proteins on a continued high protein diet, and Doeir and Berger ²⁹ observed high blood proteins in rabbits repeatedly injected with horse serum, Berger ³⁰ found that this increase is at the expense of the albumin with a corresponding rise in the globulin fraction. In his experimental animals, Letterer found only a slight increase in the total blood and globulin protein.

Clinically a hyperproteinemia has been found but rarely in generalized amyloidosis. Koref ³¹ in a case of amyloidosis secondary to tuberculosis found the blood proteins 10.89 gm per 100 cc with an albumin-globulin ratio of 20:80. There was a slight rise in the total fibrinogen. These figures are remarkable in view of the fact that in this case there was a free proteinuria. Petschacher ³² found hyperproteinemia and hyperglobulinemia in a case of amyloidosis consequent to an ulcerating tuberculosis.

As another link in the chain of his evidence, Letterer found that there is a close affinity in the molecular content of carbon, hydrogen, nitrogen and sulphur atoms between amyloid and globulin.

Until systematic studies of the blood proteins in human and experimental amyloidosis have been made, all that can be said for Letterer's contention is that it is highly suggestive. The fact that low blood proteins are found frequently in human amyloidosis does not invalidate his views because it may easily be conceived that when the amyloidosis is so far advanced as to involve the kidneys and cause proteinuria, a previously high proteinemia may be converted into a deficiency. As far as our present knowledge permits us to say the only conditions in which a hyperproteinemia and hyperglobulinemia are found with any degree of consistency are dehydration and multiple myeloma (Perlzweig, Delrue and Geschicker, ³³ Shirer, Duncan and Haden ³⁴). This latter observation made since Letterer's publication adds strong support to his contention.

DIAGNOSIS

If we may judge from the results of experimental amyloidosis in mice and the observations upon horses treated for the production of antisera amyloidosis is insidious, and does not make itself clinically manifest in man until the suppurative focus has been in existence for many months. According to Waldenstrom, ³⁵ it requires one to two years before the amyloid becomes deposited. Inasmuch as the spleen is the first organ and the one most consistently involved, enlargement of that organ is probably the first sign. As a rule, the clinician observes the patient when the disease has already spread to other viscera, especially the liver and the kidneys. Involvement of the liver never gives rise to gross evidences of hepatic insufficiency, but manifests itself clinically merely in enlargement of the organ. Sometimes the enlargement is extreme as in the case clinically reported by Rachmielowitz ³⁶ where it reached nearly to Poupart's ligament. The dominant clinical manifestations of generalized amyloidosis arise from involvement of the kidney, and indeed, most recent reports on the clinical

aspects of amyloidosis are concerned only with the renal manifestations under the title "amyloid nephrosis" We regard the term "nephrosis" as unfortunate for many reasons (1) Because under no circumstance is the amyloid kidney a pure epithelial involvement of the kidney according to the definition under which the term nephrosis was first coined, but always represents involvement of the connective tissue and vascular structures, (2) Because clinically the renal manifestations do not always correspond to the conventional criteria of nephrosis formulated by Epstein and others but are frequently accompanied by vascular reactions of which hypertension and azotemia are the prominent expressions, (3) Because in the light of modern studies, "nephrosis" is not a disease but a symptom complex whose clinical manifestations are the result of a hypoproteinemia from whatever cause The term nephrosis, therefore, if used at all should be applied to losses of protein sustained by way of the kidney

Albuminuria is the most constant symptom of generalized amyloidosis, it varies from a trace to many grams per liter As a rule albuminuria signifies involvement of the glomeruli by amyloid, but not necessarily so (Rosenblatt) On the other hand, amyloid infiltration of the kidney is not always accompanied by albuminuria When the albuminuria becomes excessive (more than 1 gram per liter) the typical secondary evidences of hypoproteinemia become manifest with anemia, edema, anasarca, cholesterinemia and doubly refractive lipoids in the urine (Rachmielowitz, Shapiro,³⁷ Noble and Major,³⁸ Bannick, Berkman and Beaver,³⁹ Rosenblatt¹⁵) Sometimes the cholesterol in the blood reaches excessive figures, in the case reported by Rachmielowitz, 625 mg per 100 c c of blood

In the majority of instances the systemic blood pressure in generalized amyloidosis is low Indeed Rosenblatt, in his large series, found no instance in which the pressure was over 140 mm of mercury On the other hand, hypertension has been observed by numerous observers (Vollhard and Fahr,⁴⁰ Bell,¹⁸ Noble and Major, Dixon) Sometimes the hypertension develops as a terminal event In the case reported by Gerber (reported previously during the lifetime of the individual by Rachmielowitz) the tension rose two and a half years after the first observation Perla and Gross report a similar observation in a patient 16 years of age The majority of observers associate hypertension with the onset of secondary renal contraction (Noble and Major)

Azotemia has been reported frequently In Dixon's series it was present in 26 per cent of the cases, it is apparently independent of the systemic blood pressure, even causing death with a normal or low tension (Bannick, Berkman and Beaver), thus differing from the usual association witnessed in the primary or secondary contracted kidney

A not infrequent symptom of amyloidosis is purpura It was present in one of my cases (Case 2) and has been reported by Königstein⁹ Perla and Gross,¹⁰ Leupold⁴¹ and Strauss⁴² Strauss reports amyloid involvement of the blood vessels of the skin in the purpuric areas

Since the introduction of the Congo red test (Bennhold ⁴³) the diagnosis of generalized amyloidosis has been placed on a sounder footing. This test depends upon the disappearance of the dye after intravenous injection of the dye. Melamed,⁴⁴ whose experience in Montefiore Hospital with the test has been extensive, regards the diagnosis of amyloidosis as justified when the retention of the dye is 50 per cent or over, doubtful when it is between 25 per cent and 50 per cent and negative when it is below 25 per cent. A retention of 100 per cent makes the diagnosis certain. Kramer and Som⁴⁵ found vital staining with intravenous Congo red of definite aid in outlining the borders of a localized amyloid tumor of the larynx. Gerber noted the persistence of the dye in the affected organs years after the Congo red test had been performed.

IS AMYLOIDOSIS REVERSIBLE?

This question is obviously important. Gardner⁴⁶ in 1891 reports the case of a man with extensive necrosis of the femur with all the constitutional evidences of amyloid disease: albuminuria, enlarged liver and cachexia. After amputation of the leg, the patient recovered completely. Walker⁴⁷ reports the case of a boy aged four, who two years after the onset of a chronic empyema developed albuminuria, enlarged liver and spleen and cachexia. A thoracoplasty was performed. One year later the liver and the spleen had diminished appreciably in size and the cachexia improved. Eight years later the boy was completely well. Waldenstrom,^{35, 48} in two publications, reports numerous biopsies of the liver upon suspected cases of amyloidosis and in three instances found complete disappearance of the amyloid after healing of a suppurative tuberculous focus. Incidentally he notes that a liver may not be enlarged and yet show considerable amyloid. Métraux⁴⁹ reports an extremely interesting observation. A child of 13 developed typical amyloid disease the result of a chronic osteomyelitis. The Congo red test was positive. The osteomyelitis healed, and five years later the Congo red test had become negative, the albuminuria had disappeared, and the liver had returned to normal size. Two years later the osteomyelitis recurred and three weeks later the patient died from sepsis. The liver showed amyloid with healing granulomatous changes, the Kupfer cells contained amyloid and the kidneys showed beginning contraction. It is doubtful whether the amyloid recurred after only three weeks' suppuration so that we must assume in Métraux's case the patient was clinically but not anatomically healed.

Recently Reimann⁵⁰ reports the case of a woman, aged 30, who developed amyloid disease two years after the first symptoms of tuberculosis and one year after a thoracoplasty. The Bennhold test showed complete disappearance of the dye after one hour. The patient slowly improved, and nine months later only a normal per cent of the dye was retained. All symptoms of amyloidosis eventually disappeared and three years later the

patient was perfectly well. The liver and the spleen were not palpable and the urine contained only a trace of albumin.

In experimental amyloidosis Kuczynski noted resorption of the amyloid if the lesion were not too advanced. Morgenstern also noted that amyloid deposits began to subside after stopping the injections of nutrose and at the end of four months had practically disappeared. In the liver he noted some connective tissue replacement. Grayzel, Jacoby and Warshall also noted resorption of amyloid in animals in the earliest stages of the process and especially if liver was added to the diet. No regression was noted in the advanced stages.

In summary one can conclude that the clinical regression of amyloidosis is possible provided the focus is removed. Whether complete anatomical healing with *restitutio ad integrum* is possible remains doubtful.

ATYPICAL AMYLOIDOSIS

This term was employed by Lubarsch to connote instances of amyloidosis in unusual sites and without apparent cause. There is usually no involvement of the liver and spleen, while such organs as the heart and lungs, the skin and striated muscles are particularly involved. Sometimes the amyloid occurs as tumor-like masses, either of pure amyloid or as a secondary involvement of a new growth (usually a myeloma). Frequently, the usual colorimetric reactions of amyloid are absent.

Lubarsch reported three cases. In the first, amyloid was deposited in the heart, lungs, stomach, esophagus, the intestines and the skin. In the second, the patient had signs of scleroderma and myotonia and a large tumor of the tongue which proved to be a massive deposit of amyloid. In the third, there was marked amyloidosis of the stomach, lungs, heart, spleen, trachea, the entire genital tract and the bronchial and mesenteric lymph nodes. Gerstel⁵¹ reports another case of huge amyloidosis of the tongue, with amyloid deposits in the skin of the neck, the gastrointestinal tract, the heart and the blood vessels. Pick⁷ reports two cases. The first, a man aged 54, had difficulty in swallowing and a generalized disturbance in muscular function. A diagnosis of myotonia, scleroderma and carcinoma of the tongue was made. Autopsy revealed a widespread amyloidosis of the muscles, the tongue, the heart, stomach, intestines, lungs and serous membranes. The second was a woman aged 51 with swelling of the tongue and muscles of the neck and thickening of the cervical skin. At autopsy there was found a diffuse amyloidosis of the tongue, the floor of the mouth, soft palate, pharynx, esophagus, stomach, intestines and diaphragm. In neither case was a cause discoverable. Recently Warren reports a case of general involvement of the musculature without involvement of the parenchymatous organs. Mollow and Lebell⁵² report the case of a man aged 60 who clinically showed hypertonia of the muscles, enlargement of the tongue, and abdominal pain. At autopsy generalized amyloidosis of the muscles and skin

was found, without involvement of the parenchymatous organs. Perla and Gross report three cases. The first was a female, 53 years of age, with extensive amyloid disease of the heart, tongue, gastrointestinal tract and other organs, who died of congestive heart failure. The second was a female aged 16 years, with extensive amyloid deposits in the kidneys, liver and suprarenals, who died in uremia. She had an ankylosis of one joint. The third case was a female, 63 years of age, with amyloid contracted kidneys who died in uremia. She had severe coronary sclerosis and a healed infarction of the left ventricle. The amyloid was limited to the kidneys. Strauss reports the case of a man, aged 72, who had dyspnea and generalized enlargement of the lymph nodes. The amyloid was found in the epi- and pericardium, lungs, lymph nodes, adipose tissue. There was a massive involvement of the muscle-free blood vessels. He discusses 28 previously reported cases of atypical amyloidosis and suggests the name para-amyloidosis to comprise these bizarre forms.

Herxheimer and Reinhart⁵³ collected 38 cases of amyloidosis of the upper respiratory tract and lung and eight cases of amyloidosis of the lung. They hold that no sharp distinction can be made between the generalized and localized forms of amyloidosis, because one may find the most extraordinary combinations.

In the atypical variety may be mentioned the tumor-like masses found in the upper respiratory tract cited by Pollak⁵⁴ and Kramer and Som.

Lubarsch has attempted to classify these atypical cases of amyloid disease into three groups: (1) Those involving mainly the skin simulating scleroderma, (2) Those in which the dominant infiltration is in the muscle simulating myotonia, (3) Those involving the tongue simulating neoplasm. In addition we would add a fourth, namely, cases of amyloidosis associated with chronic deforming arthritis. This seems the best clinical classification of so-called atypical amyloidosis at present at our disposal, but it is by no means to be considered inclusive.

SUMMARY

The chemical nature of the amyloid substance is not conclusively known. Pathologically, amyloidosis usually represents an involvement of the reticulo-endothelial system and the pericapillary and periglandular connective tissue. Almost any tissue except the cerebrospinal substance may be involved, with a special predilection for the muscles and skin. In addition to the conventionally known causes, such as tuberculosis, chronic suppuration, syphilis, Hodgkin's disease and necrotizing blastomata, amyloidosis, either general or localized, is frequently associated with multiple myeloma and its attendant Bence-Jones proteinuria and with ulcerative lesions of the bowels. A case of amyloidosis associated with chronic deforming arthritis is reported. Such an association has been reported not infrequently, though the relationship is not clear. The number of reported cases of amyloidosis

without apparent cause, in other words, primary amyloidosis, is progressively increasing and constitutes an important nosological entity. Experimentally, amyloidosis has been produced in various ways, but the underlying principle represents a prolonged overdosage with protein, preferably by the parenteral route. The evidences in favor of Letterer's contention that amyloidosis is the result of a hyperproteinemia and an associated hyperglobulinemia are reviewed and may be regarded as highly suggestive.

The clinical diagnosis of amyloidosis is dependent upon the following signs: (1) The enlargement of the viscera that may become palpable, namely the spleen and the liver. (2) The development of signs of the so-called nephrotic, but better termed hypoproteinemic syndrome consequent upon the involvement of the kidney. These are proteinuria, diminished blood proteins, hypercholesterinemia and generalized anasarca. In later stages, general arterial hypertension and azotemia may develop. The latter may occur without a co-existing hypertension, in contradistinction to other varieties of renal disease associated with hypertension. (3) Purpura of the skin. This sign has been less commonly observed but has been reported sufficiently frequently to be regarded as a symptom of the disease. (4) The Bannhoid Congo red test forms the most important confirmatory test of amyloidosis. A 100 per cent retention of the dye is diagnostic.

There is abundant evidence that amyloidosis is clinically reversible, whether it is anatomically reversible has as yet not been definitely proved. Atypical amyloidosis constitutes a diverse variety of anatomical lesions. Clinically they may thus far be classified into four groups: (1) cases simulating scleroderma, (2) cases simulating myotonia, (3) cases simulating tumor of the tongue, (4) those associated with deforming arthritis.

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ADEQUATE TESTS OF CURATIVE THERAPY IN MAN

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It is widely recognized that the subject of therapeutics has a great emotional appeal for the layman, and as a corrective measure a clear view of therapeutic possibilities is expected of the physician. But it is on the subject of therapy that the demands of practice strain the exercise of cool judgment to the utmost. The doctor may adopt either an exaggerated skepticism, or an exaggerated optimism, depending on his temperament. He is also nearly always subject to fashions in the use of certain popular methods of treatment. Due to such influences, no doubt, the element of belief as distinguished from objective data plays a large part in determining the physician's attitude toward therapeutic problems. A question that is often asked when therapeutic practice is discussed illustrates this dependence on belief. One physician asks another "Would you demand such treatment for yourself in case you were ill?" This question implies a consideration of the safety and freedom from discomfort of the therapy, but its main object is obviously to pierce beyond any facts and find the state of belief of the person who is quizzed. The profession is thus quite practical but not entirely rational when questions of therapeutic efficiency are concerned. This irrational approach persists today in spite of the fact that it has been repeatedly shown that it is possible to measure the effectiveness of curative therapy. In this paper the data accumulated in support of the value of several well known curative agents are reviewed and the experiments are cited as examples of effective methods for testing therapeutic agents. Such a discussion is not to be found in the recent medical literature. It is hoped that it will aid in defining standards of achievement for those who advocate new cures, and also contribute to a better reasoned attitude by the profession when they are confronted with reports of therapeutic success.

During the introduction of quinine, of diphtheria antitoxin, and of insulin, testing methods ranging from the most primitive to the most exact were devised and used. The experiences with these three medicaments furnish good examples of the various types of clinical therapeutic experiments that have proved most useful.

The possibility of curative therapy specific for a given disease was first demonstrated satisfactorily in the case of quinine¹ introduced to Europe in 1638. It was introduced in the form of various preparations of Peruvian Bark, in the same way that many other products of vegetable origin were made known to the medical profession in the seventeenth century. Reports of single cases or "cures" that resemble testimonials were recorded. The

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"cures" seem to have derived much of their importance as a result of the rank of the persons treated, for example, it is related that a provincial governor of Coreggidor was successfully treated later the Countess of Chin Chon, and finally in 1649 the future Louis XIV of France. The Jesuits adopted the bark and distributed it widely. It was also sold by drug dealers. Because there was little curiosity in Europe as to its source, and because the Indians who gathered it for market did not believe that it had any potency as a medicine, a good deal of adulteration and substitution occurred.

Opinion was divided as to its value for thirty to forty years. During this time and also later, the preparations of the drug frequently lacked potency. Certain prejudices of the time such as those resulting from the prevailing theories of disease processes, and from the religious character of some of the drug's supporters (as the Jesuits) prevented an impartial judgment. In 1676, Sydenham gave an account of the use of Peruvian Bark that was of a different character.² He related his observations on the use of the Bark over a period of years. He described the type of fever, namely the remittent fever, in which it was useful, the symptomatic results, and by considering dosage explained the tendency to relapse observed by others. The dosage that he recommended was quite similar to that in use today. This publication no doubt had some direct effect upon the adoption of the drug, but it was not as influential as the activities of Talbot who popularized its use as part of a secret formula which was published after his death by Louis XIV. The disclosure that Peruvian Bark formed the potent part of this formula apparently fixed its value until the present time. Much has since been learned about Peruvian Bark. The active principle was isolated in 1821, and the parasite of malaria was recognized by Laveran in 1880, but these and other facts of lesser importance have not materially altered our views in regard to its therapeutic application.

The vicissitudes of quinine from the time it was first called to the attention of Europeans until it was finally accepted are duplicated in many respects in therapeutic efforts today. Remedies are sometimes used and advocated by lay persons, medical sects, and by physicians, in the treatment of ill-defined groups of diseases, with no rational explanation of the results expected. Data may be presented in support of such claims that have no more value than a testimonial. The customary reaction to such claims is the setting up of a group that believes, and a group that does not believe, and these cannot reconcile their differences until impartial experiment determines the truth so it can be seen by all.

Sydenham's contribution to the methods of observing therapy was of the greatest importance. He showed that a skillful clinician with a knowledge of the course of a given disease, derived from experience, could observe the effects of medication and come to a valid conclusion as to its worth. This method is within the daily activity of every active and skillful clinician. It has been used more widely than any other, but the results have often been unsatisfactory. It is almost impossible to draw the boundary line between

skillful observation and the unconsciously colored reports of those who favor belief or disbelief. The personal integrity and skill of the individual author cannot be known to all of us, and without this knowledge reports of observations of symptoms as serially observed in practice cannot be evaluated. As a result, and due to the combined efforts of a long succession of physicians, improved ways of testing medicaments have been devised.

The development of further specifics such as diphtheria antitoxin dominated medical thought and progress during the isolation of many bacterial agents and the beginning of immunology in the late nineteenth and early twentieth century. The infectious theory of disease was leading to active search for curative methods in a fruitful direction. Experimental medicine was active and productive.

The steps through which diphtheria antitoxin came to the attention of the profession were as follows.³ Löffler in his description of the diphtheria bacillus noted that although it did not invade the body it produced general systemic and distant toxic effects. Roux and Yersin in 1889 showed the presence of a soluble toxin by inoculating animals with broth from which the bacterial bodies had been separated by means of porcelain filters. Von Behring, Wernicke and Futaki showed that the blood serum of inoculated animals and those recovering from the disease neutralized the effect of such toxins when passively administered in other animals. In the years 1890, 1891 and 1892 these authors described the production of such antibodies in horses, sheep and cattle, and gave methods of estimating their potency in guinea pigs. During the course of these studies, the application of this knowledge of antibodies to the cure of disease in man was kept in mind, and at Christmas time in 1891, the first child was given 50 c.c. of sheep antitoxic serum subcutaneously in the von Bergmann Clinic with a satisfactory result as reported by von Behring and Wernicke. More extensive clinical trials were made in 1892 and 1893, and the antitoxin was supplied to others and widely used after 1894.

No therapeutic measure so well tested in animals had ever before been given to clinicians for use in patients, and the lesson of the worth of carefully controlled observations led to a conscious effort to conduct clinical tests in a similar manner. Symptomatic results from antitoxin sufficiently striking to form the basis of a report like Sydenham's report on Peruvian Bark, were apparent when only a few patients had been observed. The membrane was found almost invariably to cease spreading, and to disappear, together with general improvement. The number of cases treated and described in written reports was enormous. Two new features of these reports are noted. (1) The adoption of simple statistical methods such as averages, tables and graphs to describe the effect of therapy on symptoms, on the incidence of complications and on the death rate. (2) The comparison, wherever possible, of these findings with those of control series of cases. It was widely felt that observations on large numbers of cases were better than observations on small numbers of cases because the variability of

the disease was a relatively smaller source of error in the larger series. As control series for comparison, nearly all workers used groups of patients seen in the years immediately before 1894, the year in which the general use of diphtheria antitoxin was begun.

It seemed to many that these data gathered on this unprecedented scale, and according to methods that were new in part, did not constitute an improvement over the simpler and easier studies of Sydenham. A good many criticisms were made.⁴ Most of these were concerned with the suitability of the controls seen previous to 1894 with which treated cases were compared. It was pointed out that all the cases reported were seen in hospitals, and that the character of the hospitalized cases might conceivably change from time to time due to variations in the criteria for hospitalization. Further studies outside the hospitals disposed of this objection. It was further pointed out that the treated series were diagnosed by means of throat culture, but that control cases were not so diagnosed. Analyses showed that only very small errors could arise from this source. A more serious objection to the use of controls observed before 1894 was raised by epidemiological studies. Within a few years before or after 1894 a severe world wide epidemic of diphtheria came to an end, without any relationship to the introduction of antitoxin as a therapeutic agent. The number of cases fell off rapidly, and the proportion of fatalities among the remaining cases also became less. A false idea of the effectiveness of the serum therapy had thus been gained from comparisons between cases seen before and after the termination of this epidemic. The great importance of studies in which the control observations were adequate was then acknowledged. In the best of these, by Fibiger, in Blegdam's Hospital two groups of patients were observed simultaneously in the same hospital, and chosen by means of numbers assigned impartially on entrance. In two other experiments the results of treatment were compared in two similar, but separate hospitals at the same time, in the same city, in Berlin at the Charité and the Bethanien Hospitals, and in Paris by Roux, Martin and Chaillou. Since such statistical studies of death rates are the material that is now quoted in support of this important medication, a table is given which indicates the results of several representative experiments, the first with the inadequate controls, the other three those just described.

TABLE I

Mortality Rate of Diphtheria Cases Treated with Antitoxin Compared with Cases Treated without Antitoxin

Reference	With Antitoxin			Without Antitoxin		
	Number	Number Died	Per cent Died	Number	Number Died	Per cent Died
New York ⁵	56,425	8,464	15.0	27,210	8,496	34.9
Paris ⁶	448	11	24.5	520	312	60.0
Berlin ⁷	317	53	16.7	260	102	43.1
Copenhagen ⁸	239	8	3.5	245	31	12.5

The initial venture of modern medicine into therapeutics was thus accomplished in a scientific manner. The actions and potency of diphtheria antitoxin were first carefully ascertained in animals. From these experiments the dosage of the antitoxin was easily controlled. The observation of the action of antitoxin in a consecutive series of cases according to the simple technic that Sydenham employed played a large part in its wide adoption. For written reports, however, statistical methods came into play. These gave results that were much too favorable, due to the fact that epidemic fluctuations were not observed, but the three experiments quoted above appear to have been adequately controlled. The data quoted in the above table have withstood the criticism of several critical generations.

As other therapeutic sera have been developed the same methods have been used to ascertain their usefulness in man. New variations in the application of the statistical method were often required. Antimeningococcic serum was used on a large scale first in the epidemic of 1911, and 1912, with a mortality rate (30.9 per cent) much below that always previously reported (50 per cent to 80 per cent).⁹ Since that time results have been found satisfactory by many, especially by those who have paid particular attention to the use of serum possessing the necessary type specific antibodies (Wadsworth, mortality rate 17.8 per cent).¹⁰ Dissatisfaction has been reported repeatedly by physicians who happened to see some marked variation from the average death rate in a small experience or by physicians who observed an epidemic in which the serum was not effective. It is unfortunate that no well selected series of control cases was compared with those treated with serum, as McCoy,¹¹ and more recently, Petrie¹² have pointed out. Those who have had definitely unfavorable experiences have possibly been given greater importance than they deserved. Petrie outlines the control methods that would be required for collecting the best data as follows: (1) A group of patients treated with serum. (2) A group of patients treated with frequent lumbar spinal drainage and (3) A group of patients treated intraspinally with normal non-immune horse serum. (4) A group of patients treated expectantly.

The serum treatment of lobar pneumonia may be divided into two periods in regard to the methods of testing employed. Before 1904 antipneumococcic sera were prepared without respect to the serologic differentiation among the pneumococci, and were used in small groups of cases by a large number of practitioners. The results were collected¹³ and the total was reported in statistical tables, together with each author's descriptions of the symptomatic results but with no thought of controls. The reports were favorable, but were not taken seriously, and as commonly happens with therapeutic procedures that are not definitely proved to be effective, the procedure fell into disuse, without the production of any evidence that could be shown to be unfavorable. Type specific antipneumococcic serum was shown to be clinically useful first by Cole,¹⁴ who observed a series of patients accurately after the method of Sydenham and, due to the known excellent

character of his ability and experience, these results were accepted by many, despite the lack of adequate controls. Others,^{15, 16, 17, 18} have made great efforts to compare treated patients with controls in the same hospital during the same season. In one instance¹⁹ a direct comparison was undertaken between non-specific and specific horse serum concentrates. These results, expressed by means of tables of figures, are probably the most extensive and clear of any such therapeutic investigations.

In the case of scarlet fever antitoxin the symptomatic effects were observed repeatedly^{20, 21} and were compared with adequate controls, but the naturally low death and complication rates prevented the collection of the best kind of comparable data as to its therapeutic efficiency. A further clinical experiment was conducted by Blake and Task²² that deserves special comment from the point of view of the methods of investigation employed. The clear rationale that had been provided for the use and actions of scarlet fever streptococcic antitoxin by means of the Schultz Charlton test and Dick test led Blake to inquire not only "Does the serum cure the disease?", but "Does the serum neutralize the toxin that is present and simultaneously cure the disease?" He was able to show by doing skin and neutralization tests with the sera taken at different stages of scarlet fever from 133 patients that toxin circulated in the blood stream during the time of greatest toxicity, that the toxic action of such blood was prevented by the administration of antitoxin, and that the neutralization of the toxic action of the patient's serum was followed by clinical cure of the disease. This method is applicable only where something of the action of the medicament is understood, and some essential feature of the disease can be made the object of measurement. Claude Bernard²³ early contrasted such rational experimental study of therapy in man and animals with statistical methods, presenting an array of objections to observations that were applicable to the mystical "average case." Therapeutic investigations in man such as Claude Bernard urged became of importance as the knowledge of physiology accumulated.

The most important developments in therapeutics in the recent past have been in the field of physiology as applied to medicine, by the replacement of hormones and vitamins lacking in disease. Insulin was the first of these. The methods through which its use became established are typical²⁴.

A large number of workers had confirmed and accepted Minkowski's explanation that the pancreas elaborated a hormone necessary to the metabolism of glucose. Diabetes was reproduced in the dog and carefully compared with diabetes in man. The disturbance in carbohydrate metabolism was measured by means of urinary and blood sugar, and the respiratory quotient. The discovery of Banting and Best, that watery extract of the pancreas maintained depancreatized dogs and lowered the blood sugar of rabbits, was the culmination of an extensive series of experiments by others which indicated that such a substance was present. Its application to man was a foregone conclusion. The preparation of extracts sufficiently non-toxic to be safe proved a temporary stumbling block, but this difficulty was

solved with the aid of Collip. Once a suitable concentration of the material was obtained and administered, observations of the carbohydrate metabolism showed that profound changes had been secured. Confirmation of these findings by others was all that was required to make obvious the effectiveness of the medicament. Subsequent analyses of series of such treated cases have been made with the purpose of clinical description and only incidentally to confirm the fact apparent to all that insulin is a specific remedy for diabetes mellitus. Such methods mark a definite step forward because the demonstration is conclusive and the information is not statistical. It is applicable to individual cases instead of the average case. The basis upon which such data may be developed is a clear conception of the nature of the disease.

When this search for trustworthy methods of testing therapeutic efficiency was begun it was hoped that experiments could be classified into various kinds. This has been done. Three different types of testing methods were distinguished as follows:

1. Observation of consecutive cases and comparison with the fund of experience (Sydenham)

2. Counting of cases, preparation of statistics, and comparison with similarly prepared controls (Louis)

3. Observation of the effect of medication upon some of the essential features of disease (Claude Bernard)

Outstanding successful examples of the application of each of these methods are described above. It was also hoped originally that the usefulness of each of these methods could be determined objectively from the reports in the literature. A tabulation was projected to show the results of different methods applied to the same therapeutic measure, in which only subjects about which general agreement had been obtained were to be included, with attention to the successful demonstration of the absence of effect as well as the presence of effect. Such comparisons were found to be impractical because the data were not adequate. There was a tendency for only one method to be used for each therapeutic agent, and carefully prepared reports of the lack of effect of therapeutic agents were very rare.

The statistical method is the only one of these three methods that has been the object of frequent discussion from the point of view of methodology. There are those who regard the statistical method, so called, most highly. There are others who place very little reliance upon information obtained in this way. The method in principle as Louis stated it²⁵ is quite simple. "For true experiences in medicine as I have elsewhere remarked (and as anyone may be convinced by what has preceded), true experience in medicine can result only from the exact analysis of numerous parts, well ascertained, classed according to their resemblance, compared with care, and counted." The mathematical manipulations that are useful in therapeutic experiments are of the easiest, and mistakes are rarely attributable to faulty statistical methods. Disappointing results have been obtained most often

either by investigators who have collected larger numbers of observations that were uncritically made, or by those who have not taken the trouble to secure comparable controls. The setting up of adequate controls is probably the chief technical difficulty. Experimentation on such a scale with the illnesses of people is often frowned upon. It is also the common experience that a small number of favorable results leads many of the more optimistic practical physicians to question whether it is ethical to withhold the therapy from enough impartially selected patients to provide adequate controls. The use of statistical data for judging therapeutic efficiency might become infrequent due to such complexities in its use were it not indispensable in certain situations. When the rationale of a measure is not well enough understood to provide objective evidence of cure in a single case, statistics are the only resource. Even where a thoroughly rational method of observation of the effects of therapy is known, additional information of importance such as the general death rate, complication rate and relapse rate, may be determined by means of statistics.

The classification of therapeutic testing methods used above is not exhaustive. It is obvious that the skillful use of such methods depends upon the alteration and adaptation of the technic to suit each individual disease and therapy. The value of this discussion is thought to lie in pointing out the possibility and emphasizing the desirability of careful, conclusive trials of therapeutic measures in man.

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CASE REPORTS

SPONTANEOUS SUBARACHNOID HEMORRHAGES AND THEIR RELATIONS TO RUPTURES OF SMALL ANEURYSMS IN OR NEAR THE CIRCLE OF WILLIS

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DURING recent years the accurate clinical diagnosis of the nature and localization of intracranial vascular accidents has been greatly advanced, thanks to more careful clinical pathological studies on the one hand, and to the application of the methods of cerebral angiography through the injection of thorotrast or other contrast substances, on the other. In particular, the hemorrhages into the subarachnoid space in the region of the circle of Willis with filling of the cisterna can now be usually recognized with certainty and appropriate treatment can be instituted early. The case reported here illustrates well the symptomatology and the results of prompt treatment in a case of sudden subarachnoid hemorrhage.

CASE REPORT

The patient, Beneditto M, white, 52 years of age, a contractor, was admitted to the Osler Clinic (service of Professor Warfield T Longcope) on the evening of February 1, 1936, with the complaint of severe headache that had started suddenly four days earlier in the occipital region and had gradually become more generalized and more severe.

Family History The parents of the patient are both dead, the mother having died at the age of 62. He was one of a family of six, four of whom are living and well, one having died of influenza at the age of 15. The family in general has been healthy except for a tendency to obesity. There has been no history of any disease similar to the patient's in his family.

Past History of Patient Except for measles in childhood and an attack of pneumonoma at the age of 12, the patient has enjoyed excellent health except that for many years he has had a monthly headache lasting 10 or 12 hours, apparently migraine. He denies venereal infection at any time in his life.

His habits with regard to food and drink have been abnormal. It is said that he has taken only one meal a day (in the evening). On rising in the morning he has taken one cup of coffee with two small glasses of whiskey. There has been no mid-day meal. He has been a liberal drinker of wine, consuming six or seven bottles daily in the summer time and often as many as 10 bottles daily in the winter time. In addition, he states that he has taken "as much beer as he could get." He smokes from three to six cigars daily.

He has never been operated upon and has suffered no traumata.

About one year ago his eye-sight began to fail and he was fitted with glasses.

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History of Present Illness Four days before admission to the hospital, the patient, having felt perfectly well until that time, had spent the afternoon at the movies. After supper, the one meal that he eats each day, he had not felt quite up to the mark. About 8 00 p.m. he went from the hot kitchen upstairs to a cool porch to get some clothing and on returning to the warm room he was suddenly seized with a severe, continuous, throbbing headache, beginning in the posterior part of the head and right temporal region and soon spreading over the whole of the head. He went to bed immediately, felt nauseated and tried to vomit within ten minutes after the onset of the headache. He slept some through the night but next day the headache was worse. He felt feverish, sweated profusely and found it difficult to open his eyes or to see what was going on about him and was unable to eat as food caused nausea. He could, however, retain water in the stomach. On the second day, he took 12 pills that came from a drug-store but without any relief. Indeed, the symptoms not only persisted but became intensified. There was no bowel movement during four days despite numerous doses of salts. He was not unconscious or stuporous at any time and remembers coming to the hospital. There is no history of overexertion, excitement or trauma preceding the attack.

Physical Examination (Dr. Murrick and Dr. Harvey) Temperature 101°. Respiratory rate 28. Pulse rate 56. The blood pressure was 150 systolic, 75 diastolic. The patient was evidently suffering severe pain and was so acutely ill that he was disturbed as little as possible during the examination. There was evident photophobia. The patient was somewhat obese and the skin was moist. The pupils were small and reacted well, both to light and on accommodation. There was no nystagmus and no conjugate deviation of the eyes. Examination of the eye grounds was negative. There was some deflection of the nasal septum to the right. Moderate gingivitis. Slight pharyngitis. The glands at the angle of the jaw were palpable but the glands elsewhere were not enlarged. No enlargement of the thyroid gland. There was marked rigidity of the neck and a definitely positive Kernig sign. The lungs and heart were negative. The radial arteries were palpable but not much thickened. Abdomen and genitalia negative. Deep reflexes everywhere normal. Abdominal and cremaster reflexes present. Babinski negative on both sides. There was some tenderness on pressure over all of the anterior part of the head.

Laboratory Tests Blood: red blood cells 5,330,000, hemoglobin 120, white blood cells 13,860, polymorphonuclear neutrophils 80 per cent, eosinophils 2 per cent, small mononuclears 18 per cent. Urine: Sp. gr. 1.020, trace of albumin, no sugar, a single hyaline cast seen, no white blood cells, no red blood cells. *Cerebrospinal Fluid* Lumbar puncture done in the accident room before sending the patient up to the ward revealed a cerebrospinal fluid that was under pressure of 230 mm of water. It was grossly bloody, contained 140,000 red blood cells per cu. mm. and 520 white blood cells of which 80 per cent were polymorphonuclears and 20 per cent small mononuclears. On sedimentation the supernatant fluid was yellowish (xanthochromia).

Course in the Hospital The patient was kept quiet in bed with orders for liquid diet, with limitation of the fluids to 3,000 c.c. He was given paraldehyde occasionally in 20 c.c. doses.

On the following day, February 2, the blood pressure had fallen to 144 systolic and 80 diastolic but the patient still complained of severe pains in the head. In the afternoon he was given a dose of avertin and the blood pressure afterwards fell to 130 systolic and 60 diastolic. Another lumbar puncture was done, the pressure was 210 mm., Queckenstedt negative. Red cell count in the spinal fluid 130,000. White cell count 600. That evening the patient felt much better though he was still drowsy from the sedatives. The headache had become less severe.

On February 3, another lumbar puncture was done. The fluid was blood tinged. About 8 c.c. were withdrawn. The pressure was 240 mm., Queckenstedt negative.

Red blood cells 21,000 White blood cells 420 The headache continued but was not quite so severe He was given another dose of avertin

On February 4, the patient complained of frontal headache There was no vomiting nor any significant change in respiration, blood pressure or pulse Cerebrospinal fluid (8 c c) removed at 8 00 a m showed an initial pressure of 210 mm The fluid was cloudy and of pinkish color Red blood cells 14,420, white blood cells 230

Another lumbar puncture was done at 8 00 p m The initial pressure was 220 mm About 18 c c of pinkish, slightly cloudy fluid were removed Red cell count 12,000

On February 5, lumbar puncture was done in the early morning The initial pressure was 190 mm, 7 c c of pale pinkish fluid removed red blood cells 9,700 During the day the patient improved much symptomatically The blood pressure was 140 systolic and 90 diastolic The respiratory rate 20 Pulse rate 68 He received no sedatives during that day except a little codeine At 9 00 p m another lumbar puncture was done The initial pressure was 190 mm, 10 c c of pale yellowish fluid removed The red cell count was 13,000 in the fluid

On February 6, in the afternoon, another lumbar puncture was done The initial pressure of the fluid was 60 mm, 8 c c of pale yellowish fluid removed Red cell count 130, white cell count 120

By February 7, the patient had improved so much that he said he felt himself again The headache had disappeared, he could open his eyes comfortably, the neck was no longer stiff, and the Kernig sign had disappeared Cultures from the blood and cerebrospinal fluid remained negative

Diagnosis In this case there would seem to be but little difficulty in arriving at the following diagnosis

- 1 Spontaneous subarachnoid hemorrhage, probably arising from rupture of a small aneurysm in or near the circle of Willis
- 2 Migraine
- 3 Obesity
- 4 Presbyopia
- 5 Faulty habits
 - (a) Inadequate diet,
 - (b) Potatorium

In the absence of any history of trauma, of chronic arterial hypertension, and of symptoms suggestive of brain tumor, hemorrhage into the subarachnoid space due (1) to injury of the skull and meninges from an accident, (2) to bleeding in a tumor with escape into the subarachnoid space and (3) to intracerebral apoplexy with passage of blood into the ventricles or subarachnoid space could be easily ruled out so that the diagnosis of so-called spontaneous subarachnoid hemorrhage had to be made Moreover, the sudden onset, with severe headache, nausea and rigidity of the neck indicative of meningeal irritation were strongly suggestive, and the cerebrospinal fluid on lumbar puncture confirmed the diagnosis

The fact that the patient suffered from migraine (monthly attacks) is of some interest, since some authors (especially Goldflam) have emphasized the possibility of subarachnoid hemorrhage of vasoneurotic origin, a point that I shall refer to later

INCIDENCE OF SPONTANEOUS SUBARACHNOID HEMORRHAGE

The frequency of occurrence of so-called spontaneous subarachnoid hemorrhage has only recently begun to be realized Though the condition was described as long ago as 1886 by Bramwell, it is only in recent years that the symptomatology has been studied carefully enough to permit of the recognition

of a characteristic syndrome that permits of diagnosis during life and the institution of helpful treatment promptly. Even today, many cases, especially those of milder type, are almost certainly overlooked, recovery in such milder cases by natural processes is the rule.

ETIOLOGY AND PATHOGENESIS OF SPONTANEOUS SUBARACHNOID HEMORRHAGE

Hemorrhage into the subarachnoid space due to traumatic laceration of the meninges, to hemorrhage into neoplasms that rupture to the surface, and hemorrhage because of diapedesis in blood dyscrasias are not included under the term spontaneous subarachnoid hemorrhage, in the latter the extravasation of blood into the subarachnoid space is due to spontaneous rupture of a blood vessel. As to the cause of such spontaneous rupture there has, through the years, been much discussion. Formerly, syphilis was thought to be an important cause but this idea has been shown to be erroneous, though in very rare instances syphilis may be the cause of a spontaneous subarachnoid hemorrhage it certainly cannot be a common cause.

In older patients, arteriosclerosis with chronic arterial hypertension has been thought of as the cause and in some cases this explanation has been found to be correct.

Another idea that has been promulgated is that some spontaneous subarachnoid hemorrhages may depend upon vasoneurotic influences. Thus Goldflam has suggested that the hemorrhage may be due to a functional disturbance of vasomotor control similar to what is seen in migraine, Raynaud's disease, and erythromelalgia, after abnormal vasoconstriction active hyperemia takes place and capillary oozing in the subarachnoid space results. Goldflam stated that in five of his 13 cases of subarachnoid hemorrhage the patients suffered from true migraine. It is interesting that the patient reported in the clinic today has also suffered from migraine throughout his life. A study of the bibliography of subarachnoid hemorrhage shows, however, that migraine is relatively rare in association with such hemorrhage and Goldflam's hypothesis seems to me to be untenable.

Though spontaneous subarachnoid hemorrhage may occur at any age, it is most common in young adults and is quite common in children. In recent years the idea that such subarachnoid hemorrhage depends in the main upon a primary weakness of the muscular coat of the arteries has gained ground, the very frequent association of subarachnoid hemorrhage with small aneurysms in the arteries at the base of the brain at the junction of a larger artery with a smaller branch strongly corroborates this view.

As early as 1859, Sir William Gull pointed out that small intracranial aneurysms were much more common than was usually thought and were often overlooked at autopsy since the sac is often small, thin and transparent, and the changes following rupture may easily obscure the little sac. At that time he said that whenever young persons die with symptoms of ingravescent apoplexy and after death a large effusion of blood is found, especially in the meshes of the pia mater, the presence of an aneurysm is probable.

The careful studies of C. P. Symonds (1924) also favored unrecognized aneurysm of congenital origin as the probable cause of obscure cases of subarachnoid hemorrhage.

Thanks to the exhaustive studies of Dr. Wiley D. Forbus, formerly of our department of pathology here, the origin of intracranial aneurysms of the superficial

cerebral arteries seems definitely to have been found. In a negro who died at the age of 24 with typical symptoms of spontaneous subarachnoid hemorrhage he found five small saccular aneurysms involving the left middle cerebral and the right and left anterior cerebral arteries and there had been rupture of the aneurysm of the right anterior cerebral artery into the subarachnoid space. After careful gross and microscopic studies he found that the aneurysms arose only from vessels belonging to the carotid system, that they were all located at points of bifurcation of the vessels, that there was a total absence of evidence of acute or chronic inflammation in connection with the aneurysm, that there was a definite defect in the muscular coat at numerous points of division in the right and left middle cerebral arteries, and that the location of aneurysms corresponded exactly to the location of muscular defect in the wall.

Such defects in the muscularis seem to date from embryonic life. They give rise to focal weakness in the vessel wall and may be followed by degeneration of the internal elastic membrane due to continued overstretching of that membrane, after which aneurysm can develop. Though Tuthill has attempted to refute these findings of Forbus, the majority of clinicians and pathologists interested in the subject are inclined to give full credence to the views expressed by this investigator. It is interesting that the most frequent defects in the muscularis in the arteries in the circle of Willis are at the point of junction with some branch or bifurcation, just the point at which the pressure in the blood vessel is maximal.

THE CHARACTERISTIC SYMPTOMATOLOGY OF SPONTANEOUS SUBARACHNOID HEMORRHAGE

When a subarachnoid hemorrhage is not too large or profuse, it is followed by a series of symptoms and signs that are very characteristic and make the diagnosis certain. These may be summarized as follows:

1. A sudden onset, often with a feeling as though something had "snapped" in the head and followed by severe occipital pain which later tends to become generalized.

2. Nausea or vomiting almost immediately after onset.

3. Within a few hours marked rigidity of the muscles of the neck with positive Kernig and Brudzinski signs.

4. On cautious lumbar puncture, blood will be found evenly distributed throughout the fluid in each of three successive tubes.

If these four symptoms and signs are found, the diagnosis is very easy.

When the subarachnoid hemorrhage is greater, mental confusion, agitation or even coma, may quickly follow the onset, and with very large hemorrhages there may be compression of the medulla oblongata with disturbance of respiration, marked bradycardia, and marked rise in blood pressure.

Death sometimes occurs very quickly in large hemorrhages, but if death does not occur the larger hemorrhage will be followed by bradycardia, photophobia, often choking of the optic discs, sometimes nystagmus and anisocoria, and sometimes pyramidal tract symptoms with positive Babinski sign.

Within a few hours after a subarachnoid hemorrhage the temperature begins to rise and slight fever continues for a time accompanied by polymorphonuclear leukocytosis. If later lumbar punctures are carefully done and the red cells are

allowed to sediment the clear supernatant fluid shows a definite yellow tinge (xanthochromia). The cerebrospinal fluid shows a greater number of white blood corpuscles than would correspond to the amount of blood present, indicating some inflammatory reaction on the part of the meninges. These findings in the cerebrospinal fluid in subarachnoid hemorrhage were so well described by From that but little has been added since he made his studies.

Attempts have been made to differentiate between subarachnoid hemorrhage from the anterior group of vessels (internal carotid, middle cerebral and anterior communicating arteries) and hemorrhages occurring in the posterior group (posterior communicating arteries, posterior cerebrals, basilar artery, vertebral artery). In the former, pain in the ophthalmic division of the nervus trigeminus is prone to develop, along with weakness or paralysis of the eye muscles and sometimes with exophthalmos. In hemorrhage from the posterior group, one sometimes sees hemiplegia or paraplegia, dysarthria, dysphasia, or mild cerebellar symptoms, particularly when the basilar artery bleeds.

The small aneurysms that most often give rise to these subarachnoid hemorrhages are rarely large enough to produce symptoms before hemorrhage takes place. If they should be large enough, the symptoms are as a rule neighborhood symptoms due to mechanical pressure.

TREATMENT OF SPONTANEOUS SUBARACHNOID HEMORRHAGE

If the patient is seen within 24 hours after the onset of the first symptoms (severe pain in the head, nausea and vomiting, and stiffness of the neck), the question of lumbar puncture for examination of the cerebrospinal fluid at once arises for it is desirable to decide as early as possible whether a meningitis is present or whether we have to deal with intracranial hemorrhage (either subarachnoid or intracerebral). If there be subarachnoid hemorrhage there is always some danger in making a lumbar puncture during the first 24 hours, but if it be very cautiously done a little fluid sufficient for the making of the differential diagnosis can be withdrawn without danger. If the fluid is bloody in three separate portions we can be sure of subarachnoid hemorrhage. In milder cases one will be satisfied with this for the moment, keeping the patient at rest in bed with the head elevated and administering sedatives for the pain. If the blood pressure be high, the withdrawal of from 300 to 500 c c of blood from a vein at the bend of the elbow would be indicated.

In severe cases in which a comatose condition develops quickly after onset or in which there are symptoms of compression of the medulla or pons indicating a larger outflow of blood, it may be necessary either to withdraw more fluid by the lumbar route or, perhaps better, by means of cisternal puncture as a life-saving measure, being cautious, however, not to reduce the pressure to below half the initial figure. In a few cases of severe hemorrhage, surgeons have ligated one internal carotid artery.

After the first 24 hours, cautious lumbar puncture may be done once or twice in the 24 hours with removal of relatively small amounts (3 to 5 c c) of fluid, for the relief of the pain in the head and to help in drawing off the blood from the cisternal area. Some are strongly opposed to therapeutic repetition of lumbar punctures, thinking that the value of these punctures has been over-rated and maintaining that Nature does just as well without interference, or even better

Borok goes so far as to say that lumbar puncture in the treatment of subarachnoid hemorrhage is "absolutely contraindicated", even for diagnosis he rejects it unless the clinical examination alone will not establish it, in which event he insists upon limiting the amount of cerebrospinal fluid withdrawn to 1 or 2 c.c. In our experience here, though in some cases a single lumbar puncture may suffice, in others repetition of lumbar puncture has been helpful in treatment provided the precautions mentioned have been observed.

After the acute symptoms have passed, the patient should be kept quietly in bed for at least eight weeks to permit of repair of the vessel wall, after which he may be allowed in a chair for an hour the first day, two hours the second day, and three hours the third day, then he may be allowed to walk about a little, avoiding, however, any sudden physical exertion or strong emotion. And since subarachnoid hemorrhage is prone to recur in patients who have had one attack, the mode of life should be carefully regulated ever afterward. The patient's habits should be definitely prescribed, with avoidance of any excess of alcohol or tobacco. Constipation with straining at stool should be guarded against. The prognosis is relatively good, however, and more than 50 per cent of the cases recover if treated in the way mentioned.

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PERIARTERITIS NODOSA *

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As long as the exact status of periarteritis nodosa remains undetermined it will continue to hold the attention of the profession, as it has since the first description approximately 70 years ago. Many cases have been reported in excellent detail, the pathological picture well defined, the experience of the workers abroad and on this continent completely summarized. Bacteriological studies and animal inoculations have not given uniform results. Lately the clinical side has received a major emphasis in the attempt to formulate a picture more easily recognized during life and, perhaps, at an earlier stage of the disease.

Of uncertain etiology, periarteritis nodosa seems to be related to the rheumatic group of diseases, its coexistence with rheumatic endocarditis being noted too frequently to be disregarded^{1,2,3}. Apparently divergent views, that it is due to a filterable virus, that it is a form of hyperergy to some bacterial organism, that it is closely related to rheumatic fever, may not be irreconcilable. Schlesinger and Signy⁴ have lately presented experimental evidence of a virus as a causative agent in acute rheumatism, and Swift, Derick and Hitchcock⁵ have suggested that rheumatic fever itself is a hyperergy to a non-hemolytic streptococcus. In the same patient the distinguishing marks of periarteritis nodosa and of rheumatic fever may both be found, in other instances "the lesions of small vessels in rheumatic fever are so similar microscopically to some of the pictures in periarteritis nodosa that it would be difficult to distinguish the two"⁶.

In some instances the gross appearance of the lesions permits of identification and the diagnosis has been made clinically during operation. The presence of nodules and aneurysms along the course of the middle-sized arteries gives a characteristic appearance, the arteries of the mesentery being peculiarly open to inspection. The diagnosis is often, however, made only on microscopic study and it has been established by the routine postoperative examination of specimens of the appendix, gall-bladder, kidney and vas deferens. When the disease is clinically suspected, examination of excised nodules, skin or muscle is often confirmatory, but the absence of the diagnostic lesion in the biopsy does not preclude the existence of the condition in the arteries of the internal organs where the lesions are most often found, particularly in the kidney, mesentery, liver and heart. The arteries involved are the middle-sized ones, those of the size of the coronaries and less, the large arteries and the capillaries escaping. The condition may be localized to a small area or widely distributed but, even in the latter instance, the arterial changes are not continuous along the entire length of the artery but appear at different levels, the lesion beginning and ter-

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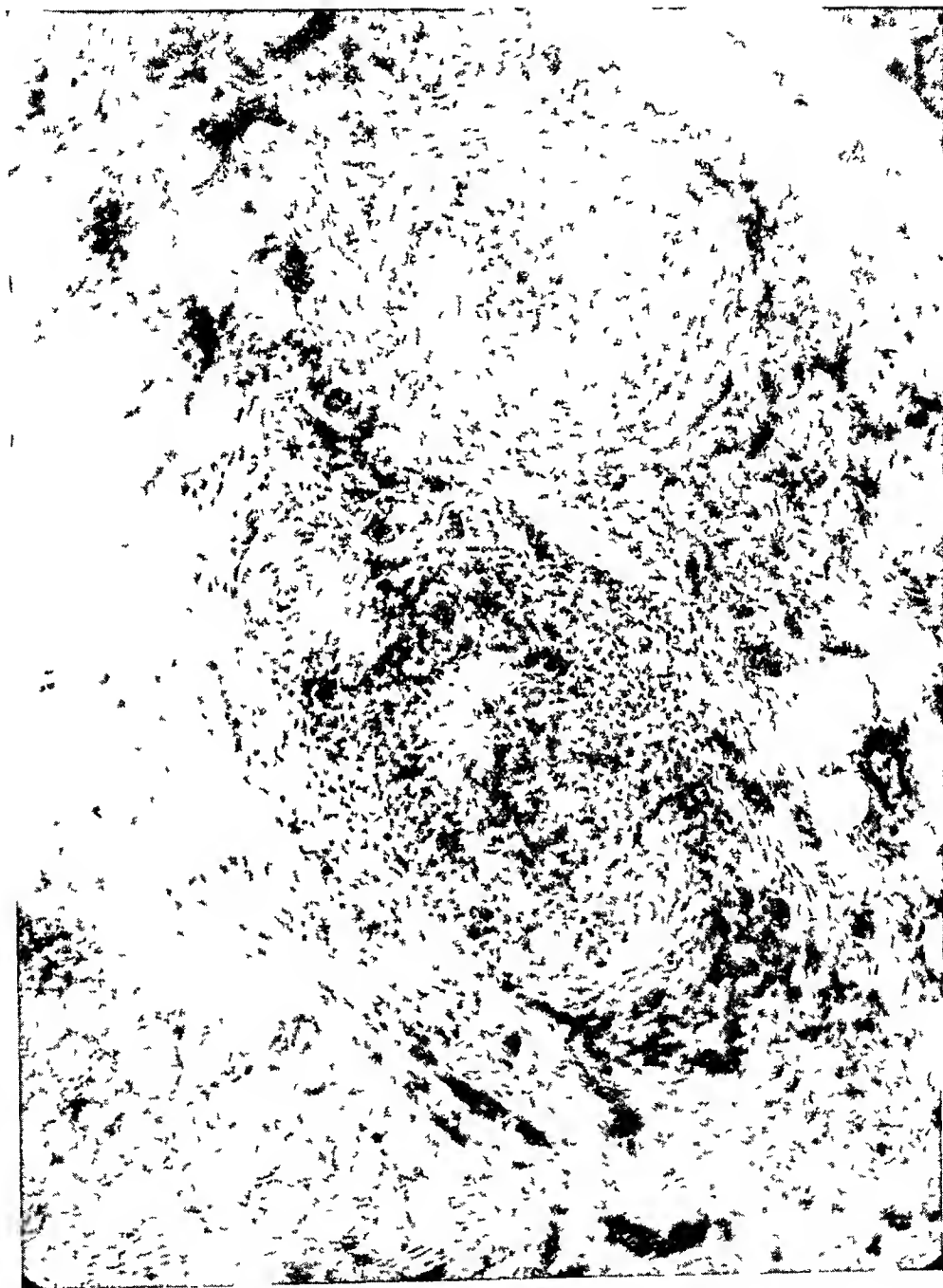


FIG 1 Advanced perivascular infiltration involving small arterioles and venule. Marked swelling and edema of intima seen in the larger arteriole.

minating quite abruptly. Apparently the toxic agent follows the periarterial lymphatics and attacks the artery at the site of entrance of the vasa vasorum. This distribution is not characteristic of periarteritis nodosa alone, Klotz⁷ having shown a similar situation of lesions in typhoid fever, *Streptococcus viridans* infection, etc. However, the character of the lesion developed in these areas is pathognomonic. The earliest and mildest lesions consist of an exudate in the adventitia—a non-suppurative inflammation. A further degree initiates the

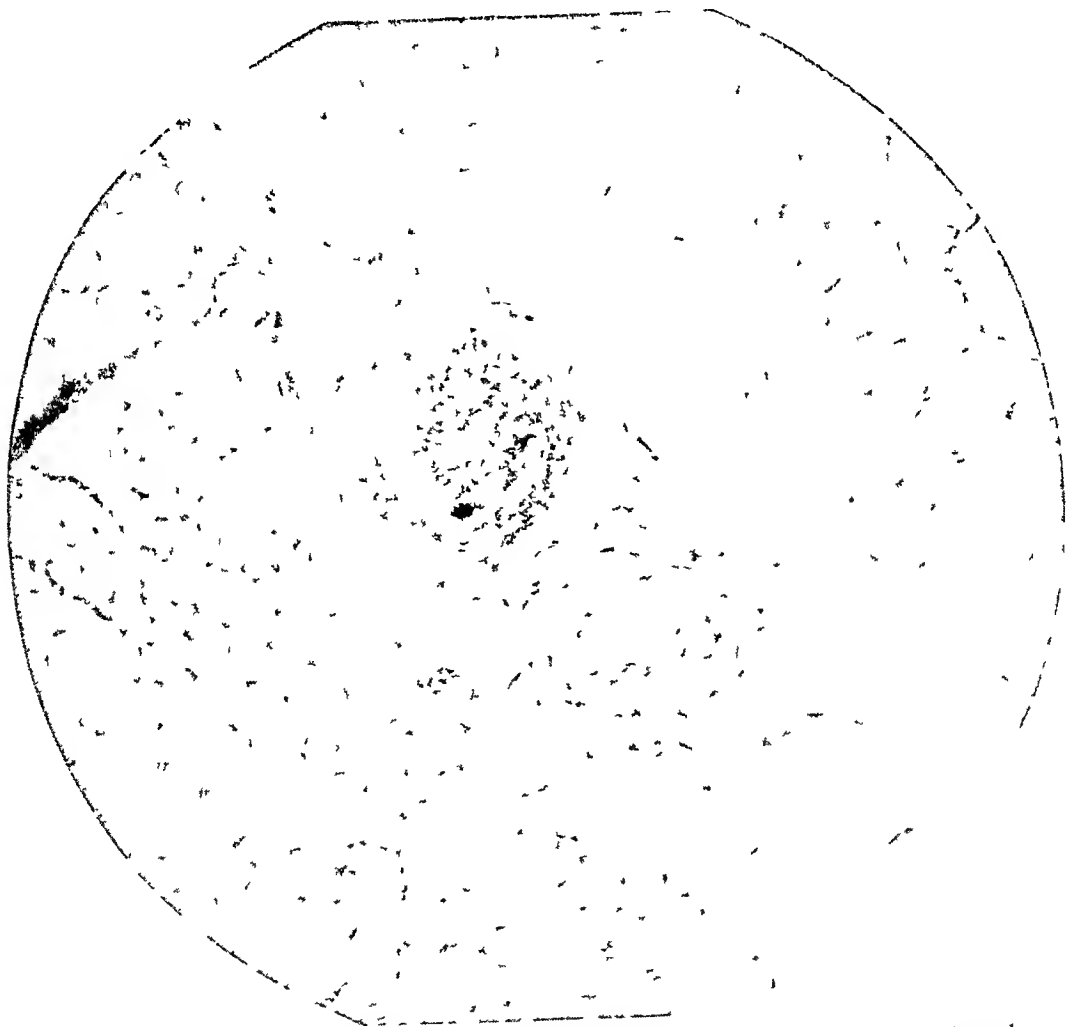


FIG 2 Hyalinized thrombus filling one small vessel and partially occluding the other

striking and typical picture, a hyaline degeneration of the media with little or no cellular infiltration. Continuation of the toxic action is followed by fragmentation of the elastica, loosening and exfoliation of the intima, weakening of the entire wall and the formation of aneurysms with thromboses of the hyaline type and canalization of the clot. Repair may take place at any stage so that fibrosis may occur before the formation of aneurysms, in which case the clinically important nodules are not formed, or, the condition may progress to aneurysmal rupture with formation of ecchymoses into the skin or fatal hemorrhage.

rhage into some of the cavities, depending on the particular arterial areas involved. The veins are sometimes affected but do not form aneurysms or nodules.

The disease is rare, Klotz finding no example in over 3,000 autopsies until two patients suffering from the disease were admitted to the hospital on the same day and went to autopsy within four weeks of each other. Lamb⁸ saw two cases within a year, but a review of the sections of all cases of nephritis occurring at the Presbyterian Hospital over a period of six years showed no case of periaortitis nodosa. Bernstein⁹ reports three cases from the Johns Hopkins Hospital and the finding of four other instances of the disease in the review of 13,000 autopsies. It is seen in children and the aged, in both sexes but most often in males in the middle years, in many races.

The recognition of the disease during life has been exceptional. At times the course is acute, of only a few days' duration, or dramatic, presenting only the picture of its surgical complications, intra-abdominal hemorrhage or intestinal obstruction, which overshadow the underlying condition. In these fulminant cases a proper diagnosis is not to be anticipated before operation. But other cases evolve more leisurely and permit a more careful review of the bizarre features. Careful analyses of the reported cases and vivid representation of the clinical pictures by students of the disorder have established criteria that permit the *intervivum* diagnosis, at least in the more fully developed stage. The basic symptoms are chlorotic marasmus, peripheral neuritis, nephritis and gastrointestinal complaints. The progressive weakness and the sense of ill-being are prominent, anemia may or may not be conspicuous. To these symptoms of multi-system disease various other apparently unrelated phenomena are added. A febrile temperature is almost always found, and edema, perhaps fleeting and not necessarily dependent, is frequently noted. Pain in the muscles and joints is usual, the pulse is often accelerated and the blood pressure elevated. Leukocytosis is practically always seen if counts are repeated, and, although eosinophilia is not always present, its occurrence is suggestive. Palpable nodules and ecchymoses may be seen along the course of the arteries, the liver is usually palpable, the spleen sometimes. Many combinations of these findings are sufficiently unusual to suggest biopsy study.

The outcome is almost invariably fatal and no more favorable reports are at hand than of those few who have gone into remission. One of Aikin's cases¹⁰ is particularly illuminating, and, at the same time discouraging, in that the patient recovered from the acute phase of the disease and four years later died from its scars—with a generalized occlusive picture, ischemia of the major organs and function impaired below the vital level. Autopsy showed no acute process of the disease. It is not unlikely that there exists a form milder than the usual fatal one but it is at present below the diagnostic level.

The manner of exitus is dependent upon the course of the disease and the distribution of the lesions. With a slow sclerosing process, the termination may be that of vascular nephritis or of cardiac failure. Most often it is sudden from arterial rupture and hemorrhage, frequently intra-abdominal, perhaps meningeal or pulmonary. The hemorrhage may be beneath the capsule of the liver or the spleen. Mesenteric thrombosis is not rare and bronchopneumonia and pericarditis have been recorded as terminal agents.

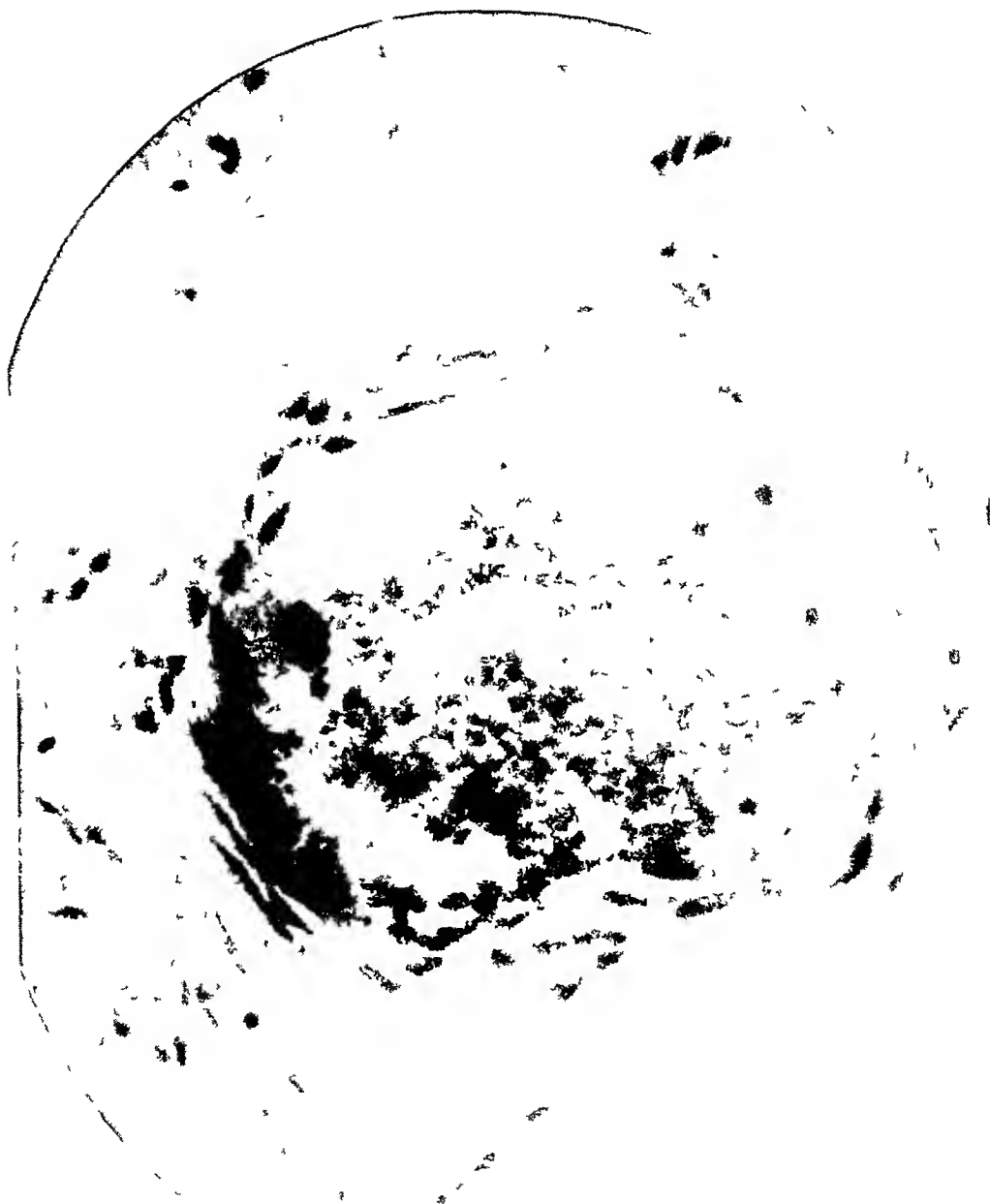


FIG 3 High power of vessel shown in figure 2, with hyalinized clot, blood cells and pigment cells

CASE REPORT

R C B, an unmarried clerk, 40 years of age, presented himself for examination at the office September 18, 1935, complaining of fever, numbness of the right foot, loss of weight, strength and endurance, and of an indescribable sense of ill-being.

Present Illness He had not felt well all spring, there had been soreness in the joints and muscles without swelling, he was constipated, and he had suffered from an attack of a perennial type of hayfever. The previous June 10 he had gone to Mississippi on vacation but felt too badly to hunt or fish according to his custom, and, noticing the fever, took quinine for two weeks without relief, he then consulted a physician who prescribed atabrine. The fever was interrupted but soon returned and persisted. He returned to his work but progressively felt weaker and less able to perform his duties efficiently. In August "the cords" above the testicles swelled for one day, on September 7 the right foot went to sleep, the ankle swelled for a few days and felt like a spasm, without injury or discoloration. The swelling soon subsided but the numbness persisted. During the summer he lost 16 pounds in weight, the temperature during this period ranging from 99 to 101° F.

Past History Raised in Mississippi, he went through measles, mumps and whooping cough. At nine years he was sent to a hospital in New Orleans with "flux." At one time, together with all his classmates who consented, he was given treatment for hookworm but he does not recall a stool examination. There was some history of malaria in childhood and he was in the University of Virginia Hospital for this condition at 18 years of age and took quinine for some time afterwards. At 23 years he acquired a specific urethritis for which he was adequately treated. For 15 years afterwards he was occasionally seen medically for partial impotence and five years ago atrophy of the veru montanum was noted. There was some question as to whether or not strong silver applications had caused the condition. At this time he expressed the opinion to the attending physician that he was becoming senile at an early age. At 22 years he first suffered from a perennial type of hay fever, followed by asthma. At that time he was working in an oil refinery, and exposure to the fumes of sulphuric acid was considered so much a factor that he abandoned his work. Six years ago he was given skin tests for the usual excitants by Dr. A. E. Greer and studied carefully. He reacted to a number moderately and a diagnosis of hypersensitiveness, respiratory, alimentary and cutaneous, was made and a diet constructed. Dr. Greer very kindly supplied the data of this examination and the laboratory and physical examinations were practically negative except as outlined. He remained on the diet for about one year, discarded it then but had no further asthmatic paroxysms. Tonsillectomy was done 8 years ago because of tonsillar infection and 5 years ago he had hemorrhoids of mild degree. He did not have rheumatic, scarlet or typhoid fever. Each winter a week's "flu" was suffered. There was little appetite and, if food were forced, a feeling of pressure and discomfort was experienced. The diet was well balanced. There had been no jaundice, no colic, no hematuria. He thought the stools were at times tarry. Best weight was 148 pounds during the war, when first seen it was 127.5. He took little exercise, but his wind was not good. He was fidgety and easily fatigued. Alcohol, tobacco and coffee were used very moderately.

Family History The father is still a locomotive engineer at 72, one brother and two sisters are living and well. The mother died at 60 of arteriosclerosis after an illness of only one week in which "brownish spots" were conspicuous.

Physical Examination A sandy complexioned man of middle age, well educated, alert and not acutely ill in appearance. Height 65¾ inches, weight 127½, temperature 99°, pulse 76.

The pupils reacted to light and distance, the sclerae and conjunctivae were clear, there was no nystagmus, no exophthalmos, no ptosis or ocular palsy. The nares were open, the facial muscles normal, no mastoid tenderness was present and there were



FIG 4 Arteriole without coagulum showing early swelling of intima and infiltration of the media and adventitia with plasma cells and lymphocytes

no tophi and no discharge from the ear. No sinus tenderness was elicited. The pharynx was negative, the tonsils had been removed with some lymphoid return. Pyorrhea, grade 1, was present, there were no devitalized teeth. The tongue was protruded in the midline without tremor or atrophy. The sinuses transmitted light clearly. The cranial nerves were negative.

There was no adenopathy. The thyroid was just palpable and otherwise negative. The spine was straight, without tenderness.

The chest was well-formed, anteriorly, the upper right lagged, the bases expanded freely, the breath sounds were of lessened intensity and no râles were heard before or after cough. The heart was not enlarged, the left border being 9 cm from the mid-sternal line. The sounds were of good quality, the rhythm regular, no murmurs were heard. There was no dyspnea, no cyanosis, no abnormal pulsations. The blood pressure on two readings was 140 mm of mercury systolic and 84 diastolic, and 134 systolic and 84 diastolic.

The scaphoid abdomen showed no surgical scars. The right kidney was palpable on deep inspiration but not tender, the spleen came down on inspiration, the tip was easily outlined and tenderness was considerable. The edge of the liver was not felt. The abdominal and cremasteric reflexes were present.

Very slight pretibial edema was noted. There was some atrophy of the calves and tenderness on pressure on these muscles. The patellars were present and normal. Vibration sense was present, as was two-point touch. No Gordon, Oppenheim, Babinski or clonus were found. Temperature and position normal. On the outer side of the right foot, below the external malleolus and extending the length of the foot, an area of hypesthesia was outlined. Likewise there was loss of acute touch sensation on the pads of the toes on the plantar surface, and in the nail region on the dorsal. No foot or wrist drop was present, station, gait and coordination normal. The patient stated that the hands went to sleep but there was no objective sign of neuromuscular disturbance.

The testes and prostate were atrophied. Nothing abnormal in the epididymis was found. Rectal examination was negative.

A casual specimen of urine was negative except for low gravity. The blood showed hemoglobin 92 per cent, red blood cells 4,580,000, white cells 11,300, with polynuclears 55 per cent, small lymphocytes 29, large lymphocytes 3, large mononuclears 2, eosinophiles 9 and basophiles 2. The Wassermann and Kahn tests were negative.

Summary This was an unusual picture, one not seen before by the examiner. The patient may or may not have had hookworm disease, he had had malaria in previous years but in the present episode he had failed to obtain expected relief from quinine and atabrine. He had had some of the common infections, he had been found allergic to certain excitants and had had rather unusual relief from asthma. A middle-aged man, with a continuous fever of three months' duration, complaining particularly of marasmus, presented symptoms of multisystem disease: asthma and tendency to dyspnea on exertion, distress after eating a meal of the usual size, and perhaps tarry stools, paresthesias and muscular atrophy, a high normal blood pressure and an increased pulse pressure, a urine of low gravity. In addition there were evanescent swellings of the ankle joint and epididymis, and there was a moderate leukocytosis and a mild eosinophilia. This picture seemed to fit in with the description of periarteritis nodosa, although no nodules had been discovered, there was no anemia and involvement of the gastrointestinal and renal systems was minimal. It was understood that trichinosis might present a similar picture but the chronicity of this case was against that diagnosis. A tentative diagnosis of periarteritis nodosa was made and on September 25 a portion of the right gastrocnemius muscle was removed under local anesthesia by Dr Herbert Poyner and the specimen given to Dr Violet Keiller for examination.

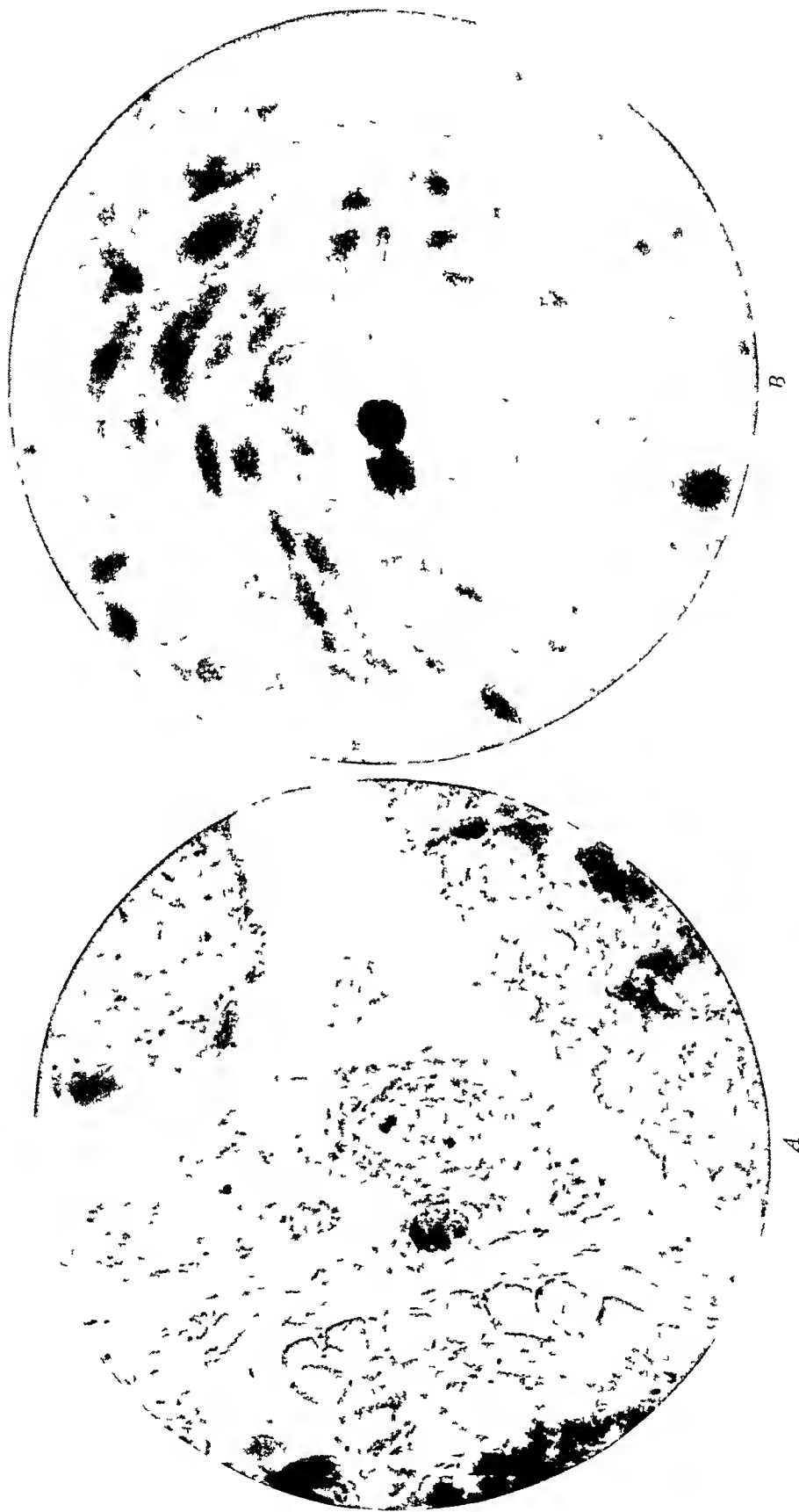


FIG 5 A and B Hyperplastic intermyofibrillar spaces with three pigment cells
 Two of these are shown in figure 5B
 Loss of striation in muscle fibers near lesion

Laboratory Studies While the sections were being prepared the following laboratory procedures were followed out. A second blood count showed leukocytes 8,900 with 7 per cent eosinophiles. All slides were negative for malaria. Blood chemistry: Icterus index 6.8, blood sugar 88.0 mg per cent, non-protein nitrogen 34, creatinine 1.72, uric acid 3.6, chlorides 520. Glucose tolerance: Fasting 88 mg per cent, one-half hour 130, one hour 149, two hours 200, three hours 154. Phenolsulphone-phthalein: one hour 50, two hours 10. Agglutination against typhoid, para A and B, abortus, proteus $\times 19$, all negative. Stool pH 7, liquid, brown, trace of bile, no blood, small amount of mucus and detritus, no ova or parasites. Prostatic smear: No pus cells, occasional epithelial cell. Basal metabolic rate plus 19. Blood culture negative. The electrocardiogram showed a rate of 68 with normal complexes.

Roentgen-ray of chest (Dr McDeed). Costophrenic angles clear. Evidence is seen of adhesions on the right dome of the diaphragm. Left dome clear cut. There is thickening of the pleura between the right upper and middle lobes. Apical regions relatively clear. No evidence of active tuberculosis or other infectious process.

Ophthalmoscopic examination (Dr Haden). "The retinal veins of the right eye were somewhat tortuous, the arteries very tortuous. In the neighborhood of the disc the artery light streaks were exaggerated, but further out in the retina they became less distinct and finally disappeared. The arteries were not sharply defined and were bordered by a fuzzy streak, which suggested a disturbance of the lymph spaces. Where the arteries crossed the veins there was a decided depression, as is seen when the arteries have become harder. One minute vessel, a vein, showed three or four minute red swellings along its course. The fundus as a whole presented a fuzzy appearance and its details were not sharply cut. The fundus of the left eye presented similar appearances of the blood vessels to those seen in the right, but not so marked. The appearances of the vessels of either eye were those seen in arterial degeneration of a moderate degree."

When the slides had been studied Dr Keiller returned a diagnosis of periarteritis nodosa. Because of the known interest in this disease of Drs Middleton and McCarter of the University of Wisconsin, slides with the history were sent there and an opinion requested. Dr McCarter wrote under date of Oct 29, in part, as follows, and his courtesy is hereby gratefully acknowledged: "The biopsy is eminently satisfactory, enough tissue having been taken to allow the pathologist to make a good examination. The larger arterioles show some reaction typical of a rheumatic infection and two small arteries contain typical lesions of periarteritis nodosa. These are fairly acute, and, in view of his present fever, I believe that a poor prognosis is justifiable."

Subsequent Course The temperature in the last week of September ranged from 98° in the morning to 101° in the evening. On October 18 the blood count showed only 3,700 leukocytes with one eosinophile. In the middle of October he was hospitalized and given artificial fever without notable beneficial result. From October 19 to November 11, the period of hospital stay, except for the periods of therapeutic fever, the temperature was of the saw-tooth, septic type, from 98.6° to 101°, the pulse not following the elevation closely and remaining between 90 and 100. The blood pressure was recorded as 142/80 mm of mercury, 160/108, it then fell to 138/80 and later rose to 170/90 on November 6. This fall in the blood pressure preceding a second rise has been commented on by Bernstein. The blood counts showed 8,200 to 10,800 leukocytes with eosinophiles 6.5 per cent and 7.5 per cent respectively. The hemoglobin dropped to 76 per cent and the red cells to 3.84 millions on November 6. Further blood cultures and subcultures were negative. The urine continued to be of low specific gravity, 1.017 being the highest and this on only one occasion. Traces of albumin were present.



FIG 6 Weigert elastic tissue stain. Fragmentation of elastica shown in arteriole. The unstained pigment cells show prominently within lumina of both vessels.

A small scarlet spot appeared on the inner side of the right calf, not nodular, not tender, becoming brown the next day. The spleen was not palpable after the first few days of observation. On dismissal from the hospital he was placed on neoarsphenamine weekly because of reported benefit from arsenic. On November 23, the blood showed a hemoglobin of 92 per cent, red blood cells 4.78 millions, leukocytes 17,300, polynuclears 85 per cent, small lymphocytes 14, large mononuclears 1 and an absence of eosinophiles. Coincidentally the temperature approached normal and remained there with only an occasional afternoon rise to 100°. The weight loss was eight pounds in three months. A second electrocardiogram was again negative. With the normal temperature there was no subjective improvement. A note on December 15: "It might be hoped from the decline in the temperature that a remission is to be expected. This is probably merely a hope for the patient has not experienced the relief from his symptoms that should accompany a true remission. He states he feels 'as if every cell and fiber of the body were sick.'" No nodules were demonstrated along the course of the arteries, in December there was a questionable one in the right pectoral muscle which was slightly tender. On December 21 he came to the office and stated that he at last thought he could detect definite improvement. He felt better and a persistent, nagging headache had disappeared. Blood pressure was 180 systolic and 100 diastolic, the temperature normal. That afternoon he was found on the floor of his living room in convulsions. These were of a generalized character, and three or four occurred in succession. He did not regain consciousness and died in the ambulance on the way to the hospital. Postmortem examination was refused.

CONCLUSIONS

A case of periarteritis nodosa is reported. This was of such chronicity and extent that a diagnosis during life could be made and confirmed by biopsy.

The striking features were the long period of comparative ill health followed by the onset of persistent fever, peripheral neuritis, muscular atrophy, renal impairment, gastrointestinal symptoms and marasmus.

The use of arsenic brought the temperature to a normal level without relief of symptoms and the disease progressed to its accustomed sudden and fatal termination.

Acknowledgment and thanks are accorded Dr. G. C. Lechenger for the photomicrographs.

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NEISSERIA CATARRHALIS ENDOCARDITIS

By R. MANNING CLARKE, M D, F A C P, and ROBERT B. HAINING,
B S, M D, *Los Angeles, California*

THAT vegetative endocarditis is due to microorganisms conveyed to the valves through the veins from external foci was first consistently proposed by Emmanuel Winge in a report to the Norwegian Medical Society in 1869. In this country, probably the first demonstration of the infectious nature of acute endocarditis was made before the Chicago Pathological Society by Christian Fenger in 1879. In 1881 Osler showed the New York Pathological Society microscopic preparations from endocardial vegetations containing minute bodies resembling bacteria. However, at this time members of the Society, while accepting the presence of the bacteria, were reluctant to regard them as the cause of the vegetations. They were inclined to believe that the bacteria were merely attendants of the disease, or possibly postmortem invaders, without pathogenic significance. Osler himself seems to have concurred with this view, though four years later his writings show that he fully recognized the infectious nature of the lesion.

Accurate determination of the causative bacteria in endocarditis began approximately at the turn of the century, and in the intervening years many organisms have been incriminated. In acute endocarditis, the principal offenders are well known pathogens, usually the pneumococcus, *Staphylococcus aureus*, gonococcus, or hemolytic streptococcus. Infrequently an organism ordinarily non-pathogenic for man is shown to be the *materia morbi*.

With the exception of the gonococcus and the meningococcus, endocarditis due to Gram-negative diplococci is rare. Examples of the disease caused by *Neisseria pharyngis sicca* have been reported by Schultz,¹ Shaw,² Graef, de la Chapelle, and Vance,³ and Goldstein,⁴ but the following case is, as far as we know, the only recorded instance in this country due to *Neisseria catarrhalis*.

CASE REPORT

History M. S., a Japanese girl, aged 15, referred by John Wahlen, M D, of Montebello, California. The patient knew of no definite childhood sickness, but once had been told she had a "leaky heart." The family history was not significant.

About October 30, 1933, she was seized with a chill, followed by fever and headache. She noticed a recurrence of these symptoms several times, and on November 25, a doctor was called who took blood for culture. This culture showed no growth, but the girl did not improve and December 7 she was admitted to the White Memorial Hospital. Her complaints while hospitalized were mainly of frequent pain in the chest and a stubborn cough with little sputum. Several times she complained of severe pain in the right upper abdominal quadrant, for which no cause could be ascertained.

Physical Examination The physical examination revealed a slightly pale, fairly well-nourished Japanese girl. On numerous occasions coarse râles were noted in the right lung base, posteriorly. The breath sounds were diminished in the left base, those heard over the upper lobes of both lungs seemed normal.

The heart was enlarged to percussion. The rhythm was regular. A loud systolic murmur was heard best over the pulmonary area, where there was also a palpable thrill.

* Received for publication March 24, 1936.

From the Departments of Medicine, College of Medical Evangelists and the Los Angeles County Hospital.

The abdomen was tender on pressure, particularly in the right upper quadrant. The uterus and adnexa seemed normal. Neurologic examination was negative.

The white blood cell count on admission was 31,250 per cu mm with 92 per cent polymorphonuclear neutrophils. The red blood cells numbered 3,600,000 per cu mm with 60 per cent hemoglobin. Urinalysis was essentially negative. Roentgen-ray of the chest showed evidence of partial consolidation in the right lower lung field. The blood Wassermann was negative. Repeated blood specimens were taken and a Gram-negative diplococcus was recovered in pure culture.

Course in Hospital Her temperature curve was septic in type, ranging from 97° F to 105° F. She became progressively weaker and toward the end somewhat delirious. She died January 12, 1934.



FIG 1 Section through vegetation from pulmonary valve showing bacterial colonies ($\times 60$)

Autopsy O B Pratt, M D performed the autopsy in an undertaking parlor where there were no facilities for weighing the organs.

The body was that of an emaciated Japanese girl. No petechiae, edema, or scars were noted.

The pleural cavities contained no fluid. Over the pleural surface of both lower lobes there were patches of fibrinous exudate. The upper lobes of both lungs were crepitant and the cut surfaces dry. Both lower lobes were heavy, dark red in color, and bloody fluid exuded from the cut surfaces. In the right lung two infarcts were found, roughly pyramidal in shape, each measuring about 3 cm in greatest length. On pressure over the lungs, purulent fluid exuded from the cut ends of the branches of the pulmonary artery.

The pericardium was smooth and glistening. The heart was only slightly larger than normal. The tricuspid valve measured 10 cm in circumference, and near the

margin of one of its leaflets there was a raised pink nodule 3 mm in diameter with a rough surface. A large, light brown, friable vegetation filled the conus arteriosus and extended 2 cm beyond the pulmonary valve into the pulmonary artery. Between the vegetation and the valve ring were two small passages, through which blood had apparently been transmitted. The cusps of the pulmonary valve were not deformed. There was slight ulceration at the site of the attachment of the vegetation, which was separated rather easily from the valve and the heart wall. The mitral ring measured 8 cm in circumference, and on one of the valve leaflets a nodular vegetation, 4 mm in diameter, was found at the line of closure. This was broken off in handling, leaving an ulcerated surface. The aortic valve appeared normal.

The liver was somewhat larger than normal and the cut surface was reddish brown. The spleen was about four times normal size. Its pulp was extremely soft and was dark red in color.

No other gross changes of significance were observed.

MICROSCOPIC EXAMINATION

Vegetation of the Pulmonary Valve Sections showed amorphous eosin staining material containing scattered leukocytes. At the free surface were fibrin and many leukocytes. Colonies of bacteria, apparently micrococci, staining lightly with hematoxylin, were seen near the surface as well as deep in the vegetation.

Tricuspid Valve Sections showed an ulcerated surface. The base of the ulcer was heavily infiltrated with leukocytes, and there were a number of bacterial colonies resembling those seen in the pulmonary valve vegetations.

Lung Surrounding an area of infarction, the alveoli were filled with eosin-staining fluid, containing some fibrin. Other alveoli were filled with blood and some were packed with leukocytes. A few colonies of bacteria were seen, each in close relation to a blood vessel. Some arteries were thrombosed and bacterial colonies were seen in the thrombi.

Liver There was evidence of marked chronic passive congestion and some fatty degeneration.

Spleen The findings resembled those of acute splenic tumor.

Kidney Some adhesions were noted in Bowman's capsule and there was an apparent increase of endothelial cells of the glomerulus. The tubular epithelium showed cloudy swelling. Some areas of interstitial tissue were infiltrated with small round cells and leukocytes.

BACTERIOLOGICAL STUDIES

All blood samples taken hourly for 24 hours on December 8 yielded pure cultures of a Gram-negative diplococcus. The number of organisms obtained varied from 1 to 3 per c.c. of blood. An identical strain of organisms was recovered in pure culture at autopsy from purulent material in the thrombosed pulmonary arteries.

On solid medium the colonies were small, rounded, firm, adherent, opaque, colorless, and at first smooth. Older colonies tended to have irregular margins and wrinkled surfaces. Subcultures were made on glucose, meat infusion agar, blood agar, plain agar, Loeffler's blood serum, and dextrose brain broth, on all of which the organism grew readily at 37.5° C. and at room temperature. No gas or acid formed in dextrose, inulin, or mannite. No pigment formed on any medium used. Except in medium containing brain, the cultures soon died, even when frequent subcultures were made. The conclusion was that the organism was *Neisseria catarrhalis*.

Accordingly the cause of death was given as acute bacterial endocarditis due to *Neisseria catarrhalis*.

COMMENT

In 1932, Curtis⁵ reported the case of a physician who, following tonsillectomy, developed acute polyarthritis. *Neisseria catarrhalis* was recovered from cultures of this man's blood and a diagnosis was made of "acute polyarthritis, acute endocarditis, and bacteremia of *Micrococcus catarrhalis* origin." The record of this patient's illness closely resembles that of a Mr L G, a white male, 21 years of age, who was admitted to the Los Angeles County Hospital, February 7, 1935, complaining of precordial pain and recurrent bouts of chills and fever. For weeks his temperature ranged from 97° F to 105.5° F, and of 11 blood cultures, eight were positive for *Neisseria catarrhalis*. A soft systolic murmur was heard at the apex, petechiae were seen on chest and abdomen, and the clinical diagnosis was acute endocarditis due to *Neisseria catarrhalis*. In contrast to Curtis' patient, who received sodium iodide, neosalvarsan, salicylates, and cinchophenic acid, this patient was given graduated doses of a *Neisseria catarrhalis* vaccine, prepared from his own blood cultures by Dr Fisk, Bacteriologist at the Los Angeles County Hospital. From April 27 to May 10 this patient remained afebrile and, feeling much better, he insisted on leaving for his home in Texas. A letter from the local social worker, dated July 4, 1935, stated that he was doing light work.

Since both these patients recovered, the diagnosis of endocarditis was not established and we believe the case reported with autopsy in this communication is the first pathologically proved example of *Neisseria catarrhalis* endocarditis in this country.

In Europe a similar autopsied case of endocarditis due to this organism has been observed and described by Endres⁶. His patient was a farm worker, 47 years of age, with a definite history of rheumatic fever, followed by heart damage. At autopsy there was evidence of rheumatic involvement of the mitral and aortic valves. (Incidentally, our patient, while giving a history of a "leaky valve," proved to have no pathological evidence of rheumatic heart disease.) Small Gram-negative diplococci were seen histologically in a vegetation on the aortic leaf of the mitral valve. Similar organisms had been recovered from blood cultures and proved bacteriologically to be *Neisseria catarrhalis*. In this case there was a classical embolic glomerulonephritis. In our patient, since the vegetations occurred on the pulmonary and tricuspid valves, embolic phenomena were seen only in the lungs.

While *Neisseria catarrhalis* is found commonly in the upper respiratory passages, and usually possesses little virulence, under favorable circumstances it apparently may become pathogenic. For example, it has been recorded as the etiological factor in meningitis,⁷ pneumonia,⁸ and septicemia.⁹

SUMMARY

A case of fatal endocarditis due to *Neisseria catarrhalis* is reported. *Neisseria catarrhalis* is rarely pathogenic, and as the cause of vegetative endocarditis it must be extremely rare, for we are unable to find another example, with autopsy, in the literature of this country.

A resumé is given of a case of septicemia of *Neisseria catarrhalis* origin. This patient was thought clinically to have endocarditis, but he made a surprising and apparently complete recovery.

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EDITORIAL

BIOLOGICAL FACTORS IN MALARIAL CONTROL

The recent sharp rise in the death rate from malaria in the United States¹ serves as a sharp reminder that the problem of malarial control in this country is not yet solved. To many of us, at least those of us who do not live in a malarial district, it is somewhat surprising to read that over 4,500 died from malaria in this country in 1934, and that the morbidity rate for that year was probably over 5,000,000 cases. Superficially the problem seems a simple one—exterminate the mosquito. Past experience indicates that any effective method of control does indeed depend on destroying the mosquito larvae or eradicating their breeding places. To accomplish this, however, we must know what species to attack, where to find it, and what weapons can be used effectively against it. Some of the complexities of this problem have been pointed out in an interesting way by Hackett².

Human malaria is transmitted exclusively by certain species of mosquitoes belonging to the genus *Anopheles*. It has been proved that about 40 (out of over 100) species may become infected with malaria and can transmit the disease to man under experimental conditions. Epidemiological studies have shown, however, that under natural conditions most of these species rarely convey malaria, and that 12 or 15 species are responsible for nearly all the malaria of the world. In a given locality, as a rule, only one or at most two or three species are of practical importance. The reasons for the failure of potential vectors of malaria to convey the disease under natural conditions are various. They can be determined only by a minute study of the habits of each species and its relation to its environment in each different region.

In some cases this depends upon the preference of the mosquito for animal rather than for human blood. In the eastern United States, for example, three potential vectors of malaria are abundant. Two of these (*A. crucians* and *A. punctipennis*) are relatively "wild" species, rarely enter houses, and by preference bite animals rather than man. *A. quadrimaculatus*, on the other hand, often enters houses, bites man and animals indifferently and is responsible for nearly all the malaria in this region. The biting habits of the same species may differ in different localities. In the case of *A. maculipennis*, the principal vector in Europe, there are several races whose habits differ in this respect. The race in the coastal districts of Holland, which breeds in brackish pools, bites both man and animals indifferently, and malaria is endemic in these regions. A few miles inland there

¹ As shown by the collected statistics of the U. S. Public Health Service and emphasized at the Symposium on Malaria of the National Malaria Committee and the Southern Medical Association. South Med. J., 1935, xxviii, 736.

² HACKETT, L. W. Biological factors in malarial control, Am. J. Trop. Med., 1936, xvi, 341-352.

is a different race (distinguishable only by the bairred markings on its eggs) which breeds in fresh water and prefers animal blood. Here malaria is sporadic. In more primitive districts in which few animals are raised (as in central Russia) this race is driven to bite man and becomes a dangerous vector. For other reasons which are entirely unknown the same species (e.g. *A. subpictus*) may convey malaria in one region (in the East Indies) and not in another (in India), although it is abundant and bites man freely in both.

The character of the breeding places is even more important. *A. quadrimaculatus* in the United States breeds in quiet fresh water in pools or puddles, and where adequate drainage of such areas is possible, the pest can be eliminated to a large extent. This should be practicable for the larger communities, at least, since these mosquitoes rarely travel more than a mile from their breeding places. In Italy, on the contrary, the prevailing species breeds equally well in quiet or flowing water, and drainage does not affect it. In certain districts of Malaya in which the vector (*A. maculatus*) breeds in open flowing streams, by damming the streams and producing a series of pools it has been possible to eliminate this variety and replace it with harmless species. On the other hand in regions like Albania in which there are two vectors which differ in their choice of breeding places, the elimination of one, when a drought dries up the pools, is accompanied by an excessive breeding of the other in the shallow streams. The breeding habits of the same species may differ in different regions. Thus in Java *A. ludlowi* breeds only in salt water, and its depredations are confined to the coastal regions, while in Sumatra it breeds in fresh water and infests much of the island.

A radical change in the environmental conditions in a district may convert a potential vector, previously harmless, into a dangerous transmitter. This occurred when the cultivation of rice was introduced into Sumatra during the war. An epidemic of malaria broke out promptly, due to *A. hyrcanus*³. This possibility had been excluded, it was supposed, by the fact that this species breeds abundantly in the rice fields of Java and other neighboring islands and there it is not a transmitter.

In the United States the problem seems relatively simple. There is only a single important transmitter, and its breeding places can be eradicated without undue difficulty. The immediate obstacle is the prohibitive cost of carrying out such procedures on an adequately large scale. It is to be hoped that further study will reveal less costly methods of control. Unless it does, we may expect that malaria will continue, at least until the economic value of the peasant exceeds the cost of the public health measures necessary to protect him.

P C

³ SWELLENGREBEL, N. H. Le medecin et l'entomologie, Riv. di Malariol., Sez. II, 1934, vii, Supp. to No. 3, 73.

REVIEWS

American Martyrs to Science Through the Roentgen-Rays By PERCY BROWN, M D ,
F A C P , F A C R 276 pages, 15 5 × 23 5 cm Charles C Thomas, Baltimore
1936 Price, \$3 50

This small volume presents a brief sketch of the lives of an heroic group of Americans connected with the early history of the roentgen-rays. It is written in a readable style and brings to life those earnest, faithful scientists who, by every sacrifice, including that of life itself, made the advance of roentgenology possible.

Forty years ago this new science was conceived and it has been largely due to the valiant efforts of this illustrious group of men that roentgenology has advanced so rapidly to its present status. It is interesting to note the different channels by which these men entered the field, and their complete absorption in their work, even when suffering the most excruciating pain. Very few of the early pioneers were provided with any protection against the direct effect of the rays. Sometimes the face and chest, and more often the hands, were repeatedly exposed in order to make a satisfactory examination of the patient, or to exploit the "x-rays" in popular exhibitions.

The serious nature of their work so thoroughly dominated their thoughts that they had little consideration for their personal safety. These pioneers lived and died in relative obscurity. They gave their lives to the cause of science, and if ever the term Martyr should be applied, it belongs to them.

The author has inserted a simple glossary for the layman "to clarify the meaning of certain scientific terms impossible to avoid."

The author speaks with authority and modestly refrains from any personal allusions. Anyone interested in the progress of medicine will find this book both interesting and instructive.

H J W

The Pathology of Internal Diseases By WILLIAM BOYD, M D , M R C P , F R C P
Second Edition 904 pages, 16 × 24 cm Lea and Febiger, Philadelphia
1935 Price, \$10 00

In the second edition of this work the author has added many new sections, and major alterations have been made in other sections. The illustrations are excellent. References, especially to the more recent literature, follow each chapter. The author not only describes the morbid anatomy of internal diseases, but also links it to the clinical symptomatology presented by such diseases. At times he perhaps is more positive in his statements than would seem justified by the evidence at hand, and at times the clinical discussion leaves something to be desired. However, one hesitates to criticize what the reviewer considers so valuable a work. The style is forthright and the book throughout maintains its interest. It is highly recommended to students and to practitioners.

W S L , JR

Common Contagious Diseases By PHILIP MOEN STIMSON, A B , M D 437 pages,
14 × 20 cm Lea and Febiger, Philadelphia 1936 Price, \$4 00

The clear presentation of the subject matter contained within this manual is striking, for despite its conciseness, the author has avoided disjointed sequences and the impression of incompleteness that a reader is so often left with after reading abbreviated books. There is instead a personal feeling instilled so that the reader may easily imagine himself in the presence of the author.

The introductory chapter on "Infection and Immunity" is discussed mostly from its clinical relationship. The author deals understandingly with these topics, without becoming mired in hypothetical conjectures.

Diphtheria, Vincent's angina, scarlet fever, measles, rubella, pertussis, mumps, chicken-pox, small-pox, meningococcus meningitis and poliomyelitis are the diseases discussed as contagious. All aspects of these conditions are dealt with in an adequate manner. The newer work on the subjects is included and a practical critical evaluation offered. Adequate space is devoted to the various sera being used in both prophylaxis and treatment. Personal experiences are nicely blended in the discussion to confirm or throw doubt upon a conjecture. An adequate bibliography is included at the end of each chapter. A final chapter on the "General Management of Contagious Diseases" is included. And here, especially in the discussion of the management of "Contagion in the Home," is the practical attitude made most apparent.

Photographs and various charts are embodied in the text. Unfortunately the photographs of the exanthems are not colored, hence their value is relatively negligible.

The book is unreservedly recommended by the reviewer for the use of the medical student and practitioner.

J E B

The Human Foot By DUDLEY J MORTON 244 pages, 16 X 23.5 cm Columbia University Press, New York 1935 Price, \$3.00

This book is a most complete treatise on the foot and to a practicing orthopedist is most timely. If it should be read by a sufficient number of medical practitioners, shoe manufacturers, and chiropodists its value would be inestimable.

The book is divided into three parts, covering the evolution, the physiology, and the functional disorders of the human foot. Each part treats thoroughly the various elements of its topic by means of several or more chapters. The text is easy to read, is as free from technical language as is possible, and yet is thoroughly clear and easy to understand.

Part 1 is quite interesting and explains what may lie back of many functional foot disorders. Ordinarily, we rarely realize that the foot of today is expected to do many things for which it originally was not made and this particularly with the handicap of the modern shoe.

Part 2 analyzes thoroughly the varied and complicated activities of the foot in standing, walking, etc. Emphasis is laid upon the well known fact that a normal foot does not need "artificial aid in its function of stance and locomotion." People who have never worn shoes do not as a rule have the foot troubles we hear so much about. This chapter bears analysis and study and will well repay a careful reading. Active exercise is essential to foot comfort and efficiency.

Part 3 considers the possible effects of abnormal development and function, describes the clinical signs and symptoms of each type of disability, and lastly gives good suggestions as to treatment. Emphasis is laid upon the improper use of an arch support, especially of the rigid type. Redevelopment of the weakened structures is the theme of this section and this should be the basis of sound practice. Artificial aids should be used only as auxiliary measures until proof exists that the foot will not respond and must be "crutched" permanently.

All in all the book should be referred to frequently and should find a place in everyone's reference library.

A V

The Kidney in Health and Disease Edited by HILDUNG BERGLUND, M D, and GRACE MRDES, Ph D with the collaboration of G CARL HUBER, M D, WARFIELD T LONGCOPE, M D, and ALFRED N RICHARDS, Ph D, M D 754 pages, 16 X 24 cm Lea and Febiger, Philadelphia 1935 Price, \$10 00

This volume is the outgrowth of a symposium in 1930 on the structure and function of the kidney in health and disease. The project was initiated by Dr Hildung Berglund, then Professor of Medicine in the University of Minnesota. The contributions made at that time have been revised and brought to date by the participants in the symposium. There are 44 contributors and listed among them are many of the prominent investigators of questions pertaining to the kidneys. The book is divided into six parts and 41 chapters. The main divisions are concerned with the anatomy and physiology of the kidney, clinical aspects of renal functions, Bright's disease and other pathologic renal conditions, albuminuria and edema, ocular changes in Bright's disease, and clinical aspects of Bright's disease.

This volume affords an excellent example of what may be accomplished by welding together contributions by many outstanding investigators. It is an authoritative reference work. Each contribution is accompanied by a thorough bibliography. This is a volume which no one interested in kidney problems will wish to be without and any practitioner could read it with pleasure and profit.

W S L, JR

The Crippled and the Disabled By HENRY H KESSLER, M D 337 pages, 16 X 23 5 cm Columbia University Press, New York 1935 Price, \$4 00

Any study of the problem of the crippled and disabled is necessarily extensive and difficult due to the many types and combinations, both as to areas and senses involved, and to the age periods and variable reactions of each. Dr Kessler has very thoroughly reviewed the extensive available literature and has analyzed the facts presented from an unbiased standpoint. His suggestions for the correction of the situations as now found are sensible and sound.

The book is divided into seven parts, an appendix and a large bibliography. The disabled are considered generally in Part 1, where the problem as a whole is analyzed with appropriate comments as to the need for a change in the attitude of the disabled toward the community and vice versa.

Part 2 deals with the child problem both here and abroad. Much more definite progress has been made for children than for adults due to the appeal possessed by children and to the activities of fraternal and social organizations. Industrial advancement and the experiences of the War have led to a greater activity in providing care for disabled adults.

Parts 3 and 4 consider the industrially disabled and those injured in war. The care of these two groups has stimulated the development of improved physical and occupational therapy. Statistical tables and many references show the changing situations of these types. An appeal is made for a more universal consideration of the disabled by industry so that a trained cripple may obtain reemployment more easily.

The chronically disabled are considered in Part 5. Special emphasis is laid upon how their needs are and should be met.

The blind, deaf, and deaf-mutes are considered very briefly in Part 6, and the whole picture is summarized in Part 7.

An appendix gives a short summary of the various types of legislation in each State, at the end is a very complete and extensive bibliography which will be most useful to anyone who is interested in the problem of the disabled.

The book is an important addition to a reference library and is very appropriate at the present time.

A V

COLLEGE NEWS NOTES

ADDITION TO THE LIFE MEMBERSHIP ROSTER

Dr Orville H Brown (Fellow), Phoenix, Ariz, became a Life Member of the College on June 10, 1936

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following gifts to the College Library of publications by members

Dr J N Hall (Fellow), Denver, Colo—4 books, Volumes I and II, "Borderline Diseases," and Volumes I and II, "Textbook of Legal Medicine and Toxicology",

Major James S Simmons (Fellow), M C, U S Army—1 book, "Laboratory Methods of the United States Army" (Fourth Edition),

Dr Charles F Morsman (Fellow), Hot Springs, S D—2 reprints,

Dr Glenn D Carlson (Associate), Dallas, Tex—1 reprint,

Dr John P Hilton (Associate), Denver, Colo—1 reprint

MEETING OF THE NEW JERSEY MEMBERS

Under the Governorship of Dr Clarence L Andrews, Fellows and Associates of the College from New Jersey held a luncheon-meeting at the Claridge Hotel at Atlantic City on June 3 Dr Andrews acted as Chairman and Toastmaster Dr Ernest B Bradley, President of the College, Lexington, Ky, Dr O H Perry Pepper, First Vice-President, Philadelphia, Pa, Dr William D Stroud, Treasurer, Philadelphia, and Mr E R Loveland, Executive Secretary, made short addresses concerning various College activities Other guests present included Dr E J G Beardsley, of Philadelphia, Governor for eastern Pennsylvania, and Dr Lewis B Flinn, of Wilmington, Governor for Delaware Twenty-five Fellows and ten Associates from New Jersey were present

Dr George R Minot (Fellow), Boston, Mass, and Dr Hugh J Morgan (Fellow), Nashville, Tenn, were elected Vice-President and Secretary, respectively, of the Association of American Physicians at its annual meeting in Atlantic City, May 6

Dr W A Dearman (Fellow) has removed from Gulfport, Miss, to Whitfield, Miss, where he has assumed the duties of Assistant Superintendent of the Mississippi State Hospital

Dr Ralph Pemberton (Fellow), Philadelphia, addressed the Lehigh County (Pa) Medical Society at Allentown, April 14, upon Arthritis, he gave a Seminar at the Robert Packer Hospital, Sayre, Pa, May 27, on Arthritis, and he addressed the Medical Society of the County of Saratoga, New York, June 4, upon the same subject

Dr Joseph Hajek (Fellow), New York, N Y, has been elected Secretary of the Section of Medicine of the New York Academy of Medicine

Dr Hyman I Goldstein (Associate), Camden, N J, presented a paper on "Antispasmodic Therapy in Gastro-Intestinal and Biliary Tract Diseases" at the 170th annual meeting of the New Jersey State Medical Society, Section on Gastro-Enterology, at Atlantic City, June 4 His paper was discussed by Dr Samuel Weiss (Fellow), New York, and by Professor Charles M Gruber, of Philadelphia

Dr Goldstein also discussed constipation at the convention of the National Society for the Advancement of Gastro-Enterology at Atlantic City, June 5

At the annual meeting of the Arkansas Medical Society at Hot Springs National Park, Dr George B Fletcher (Fellow), Hot Springs National Park, was installed as President Dr Arthur G Sullivan (Fellow), Hot Springs National Park, was elected a Vice-President and Dr William R Brooksher (Fellow), Fort Smith, as Secretary

Dr Leon Unger (Associate), Chicago, addressed the Chicago Society of Allergy, May 18, on "Asthma in Children, Results of Treatment"

Dr William H Marshall (Fellow), Flint, Mich, has been elected President of the Northern Tri-State Medical Association

Dr James H Donnelly (Fellow), Buffalo, is President of the Buffalo Academy of Medicine

Dr Walter W Palmer (Fellow), Dr Alvan L Barach (Fellow), both of New York City, were lecturers on the program of the ninth annual postgraduate day of the Mahoning County (Ohio) Medical Society at Youngstown, April 30

Dr Edgar A Hines (Fellow), Seneca, S C, has been reelected Secretary of the South Carolina Medical Association Dr Hines has served as Secretary for 26 years

Dr Howard T Karsner (Fellow), Cleveland, Ohio, has been elected Secretary of the American Association of Pathologists and Bacteriologists at their annual meeting in Boston during April

Dr Jesse D Hamer (Associate), Phoenix, Ariz, was installed as President of the Arizona State Medical Association at its annual meeting recently

Dr Charles Wolferth (Fellow), Philadelphia, delivered a lecture on "Observations on the Mechanism and Clinical Interpretation of Heart Sounds" in connection with the annual postgraduate course of the Indiana State Medical Association at Indianapolis during April

Dr George P Pratt (Fellow), Omaha, Nebr, presented a lecture on coronary disease at the regular meeting of the Southwestern Iowa Postgraduate Medical Society in the spring

Dr Soma Weiss (Fellow), Associate Professor of Medicine at Harvard Medical School, was one of the speakers on a cancer symposium conducted in connection with the 84th annual session of the Maine Medical Association in Rangeley, June 21 to 23

Harvard Medical School will observe its Tercentenary, September 14 to 15. The Harvard Medical Alumni Association will hold its annual meeting and dinner in Vanderbilt Hall on the evening of September 15, the dinner having been postponed from its usual time in June to encourage participation of as many graduates as possible in the Tercentenary celebration. Dr George R Minot (Fellow) will act as Chairman of a symposium on nutrition and the deficiency diseases, Dr James H Means (Fellow) will act as Chairman of a symposium on the endocrine glands.

The Medical Society of New Jersey held its 170th annual meeting at Atlantic City, June 2 to 4, under the Presidency of Dr Marcus W Newcomb (Fellow), Browns Mills. Among guest speakers were Dr Israel M Rabinowitch (Fellow), Montreal, "Medical Complications in Diabetes Mellitus," and Dr Arthur C Christie (Fellow), Washington, D C, "Medical Progress Under the Leadership of the Medical Profession."

Dr Ross McC Chapman (Fellow), Towson, Md, was elected President-Elect of the American Psychiatric Association at its annual meeting in St Louis, May 4 to 8.

Sir Frederick G Banting (Fellow), Toronto, and Dr Joseph B Collip (Fellow), Montreal, addressed the annual meeting of the Canadian Medical Association at Victoria, B S, June 22 to 26, on "Silicosis Research" and "Significance of Recent Investigations of the Ductless Glands," respectively.

Dr F M Pottenger (Fellow), Monrovia, Calif, presented the Phi Rho Sigma Lecture at the University of Colorado School of Medicine, Denver, May 7, on "Physiological Approach to the Diagnosis and Treatment of Tuberculosis."

The Academy of Medicine of Washington was organized April 28, with Dr William A White (Fellow), President, Dr Earl B McKinley (Fellow) and Dr Matthew W Perry (Fellow) as Directors. The membership will be limited to 60 resident members and 30 associates or non-resident members. Membership is open to non-medical as well as medical men, since no special distinction has been made between the medical sciences and allied sciences.

Dr Guy C Jarratt (Associate), Vicksburg, Miss, has been elected one of the Vice-Presidents of the Mississippi State Medical Association.

Dr Edward Rose (Fellow), Philadelphia, addressed the Gloucester County (N J) Medical Society recently on "Basal Metabolism and Its Relation to Disease."

Dr Louis E Viko (Fellow), Salt Lake City, is President-Elect of the Utah State Medical Association.

OBITUARIES

DR GERTRUDE M JOHNSON

Dr Gertrude M Johnson died January 29, 1936, of lymphatic leukemia, aged 56 years.

Dr Johnson was born in Minneapolis, Minn, December 12, 1879. She entered Battle Creek Sanitarium in 1898 in the School of Nursing, graduat-

ing in June 1900 She began the study of medicine in the American Medical Missionary College in 1900 and graduated in 1904, and since that time has been employed almost constantly as a member of the medical staff of Battle Creek Sanitarium

In addition to her medical staff duties, she devoted time for several years to teaching in the School of Nursing During her career in medicine she made two rather extended visits to Europe for postgraduate work, visiting both England and the Continent

Dr Johnson was a keen observer and diagnostician In addition she devoted considerable time to research work, and produced several articles of value during the last few years She completed a report on an interesting case during her last illness

She was a member of the American Medical Association, of the Michigan State Society, of the Calhoun County Society, and also a Fellow of the American College of Physicians She was greatly beloved by her patients, many of whom came to see her year after year because of the kindly interest she showed and the effort she made to neglect nothing that might afford them relief

M A MORTENSEN, M D , F A C P

DR CARL FREDERICK MOLL

Dr Carl Frederick Moll of Flint, Michigan, an Associate of the College since 1926, died suddenly of a heart attack in Detroit on May 1, 1936, at the age of 64 years

Dr Moll graduated from the Saginaw Valley Medical College in 1899, and started practice in the Upper Peninsula in Michigan Shortly before the war, he moved to Flint, Michigan, and practiced as an internist in that city since that time

Besides enjoying one of the largest practices in his city, Dr Moll found time to give much to the medical organizations of the state and nation He was Past President of the Marquette County Medical Society, and held numerous offices in the Michigan State Medical Society, including that of President From 1926 to 1935, he was a member of the House of Delegates of the American Medical Association His professional appointments were numerous He was a member of the staff of St Joseph's Hospital and of the Women's Hospital, as well as being President of the Staff of Hurley Hospital, and Physician to the Michigan Home of the Deaf

Dr Moll was well known both as an internist and as a citizen of the state A man of warm friendliness and unselfish loyalty, he was well beloved by all of his fellow physicians, who will miss keenly his wise counsel and able leadership

HENRY R CARSTENS, M D , F A C P ,
Governor for Michigan

MINUTES OF THE GENERAL BUSINESS MEETING

DETROIT, MICH

March 5, 1936

The Annual Business Meeting of the College was called to order at the Book-Cadillac Hotel at 5 00 p m, Thursday, March 5, 1936, with President James Alex Miller presiding. Reading of the Minutes of the previous Business Meeting was dispensed with by resolution.

Dr William D Stroud, Treasurer, presented the following treasurer's report

"At the present time our total funds amount to \$157,329 00. This is distributed into Endowment, \$58,281 72 and the General Fund, \$99,047 47.

"The funds have been audited and the accounts declared correct by a certified public accountant. Our investments as originally purchased, in bonds, amounted to \$111,844 00. Their present value, as of February 28, is \$116,430 00, or, in other words, they show a book profit of \$4,285 00.

"Our stock investments amount to a purchase price of \$14,811 00 and their book value at present is \$17,902 00, showing a profit of \$3,091 00. Our bonds and stocks have increased in value \$7,377 00 since they were purchased. I think this gives the members of the College a very secure feeling as to our finances."

The treasurer's report was accepted and filed.

Mr E R Loveland, Executive Secretary, reported that up to this time 1,528 had registered at the Annual Meeting. He gave the following report on membership.

"During the past year 181 Fellows and 187 Associates were elected. That does not mean that the College has grown 368, because many of those elected to Fellowship were advanced from Associateship.

"During the past year, the Executive Offices had published the 1935 Directory containing the names of 5 Masters, 2415 Fellows and 818 Associates, total, 3238. Since the publication of the Directory on October 1, 1935, there have been 19 deaths, 10 resignations and 16 were dropped for delinquency (the number of resignations and the number dropped for delinquency was called to the attention of the general body, because the number was so small in comparison with the membership), 13 Associates were dropped for failure to qualify for Fellowship. With these elections and adjustments, the membership at this date was 4 Masters, 2565 Fellows and 843 Associates, total, 3412."

Mr Loveland reported that since the rule has been in effect that new candidates must first become Associates and serve a probationary period of three to five years, over 75 per cent of such Associates had qualified for Fellowship. Of the class of Associates elected in 1931, 78 qualified for Fellowship and 23 failed for one reason or another. In other words, about 77 per cent of those elected in 1931 succeeded in becoming Fellows.

In regard to Life Members, he reported that there had been a further increase, the number having reached 61 to date. He referred to the Life Membership Roster being displayed at the College Booth near the registration headquarters.

Mr Loveland further reported that a fairly large number of members visit the College Headquarters each year, and that in some instances he had been able to arrange programs of a medical character for visiting members, so that they could observe what is being done medically in Philadelphia. He invited members to visit the College Headquarters and to call on the College Offices for any assistance whatsoever that can be rendered. He thanked the members of the local Detroit committees who had helped so greatly in making the arrangements for the Detroit Session.

Dr James Alex Miller, President, on behalf of the Board of Regents, reported first upon the progress toward the establishment of an American Board of Internal Medicine for the certification of internists, that work had been organized under a joint committee of the American College of Physicians and the Section on the Practice of Medicine of the American Medical Association, the details having been worked out to such a point that the Board of Regents of this College had approved them, as far as the College was concerned, and the Committee was authorized to proceed. All that was necessary was the final approval of the American Medical Association, whereupon the Board will be ready to proceed with the regular installation of a method of certification of internists in this country. He expressed the prophecy that this will mean a long step forward in defining what internists really are and what specialists in Internal Medicine should be. He expressed the opinion that the work of this board will be of great help to the College in enabling it to make these examinations as a basic requirement for Fellowship. The work of this board will not in any way interfere with the activities of the College. Certification may be one of the requisites for admission to the College, but the College will undoubtedly always have other requirements for its Fellowship. This development will have a great influence in raising the standards of the practice of Internal Medicine in this country, the work of the College during the past year in sponsoring this board may be looked upon as of real significance.

The second subject discussed by President Miller concerned the finances of the College and various projects concerned therewith. He informed the members that over past years the College has been successful in accumulating a sum of money somewhat in excess of immediate needs. The Board of Regents has given serious consideration to this and has a definite program in mind, a program which in the future will enable the College to extend its usefulness and possibly at some future time to diminish definitely financial burdens of members, particularly in respect to initiation fees, which at present are \$80.00, having already been reduced from \$100.00. The College has been enabled to sponsor the American Board of Internal Medicine, because it had some available money. The College is going to finance all of the Board's work during the stage of its development, advancing the money until the Board is able to return it from the fees which will be exacted from those who take the examinations, and the College also has a plan of extending its other activities as it has financial opportunity to do so. Among these other activities may be the stimulation of clinical research among younger members of the profession by establishment of additional fellowships, also probably by the procuring of a suitable and dignified permanent home for the College. Furthermore, the Board of Regents has provided for the appointment of a committee to look into the details of other methods for the promotion of Internal Medicine. The procuring of a suitable home for the College will ensure permanency and add dignity to the organization. In conclusion, Dr. Miller expressed his appreciation of the cooperation the membership had shown in the arrangement of the Detroit Session, and for their interest and hearty cooperation during his term as President. He especially complimented the staff of the Executive Offices, the Executive Secretary, the Treasurer and the Finance Committee, stating it is due in no small measure to their efficient management that the College now finds itself in a position to expand somewhat in its field of usefulness in Internal Medicine. In conclusion he said in part:

"Now, personally, I wish to express again my own very deep feeling of appreciation of the great honor that you have conferred upon me in electing me to this office of President. It has been a year which has been most interesting and stimulating and one which I shall always remember with the greatest pleasure and which will always be a source of great satisfaction and will make me feel that, in being honored to be your President, there has been a year of productive effort and one of great satisfaction which I will always carry with me.

"I now come to a very pleasant duty as I lay down the responsibilities of the Presidential office. It is with very peculiar pleasure that I have the privilege of in-

ducting into office the incoming President We have in our new President a man whom we all love, a man who is outstanding in his devotion to the best interests of the practice of medicine, a man who has given, both in the Board of Governors and in the Board of Regents, the best that he has to the interests of this College We know what Ernest Bradley has been and, consequently, we are confident of what he will do for this College It is therefore with the greatest pleasure and happiness, Dr Bradley, that I turn over the responsibilities of this office to you" (Applause as all stand)

President-Elect Bradley "It really seems impossible that the time should ever come that I could stand here as your President, after the renowned men who have preceded me Of course, to those other men who have been elected as President, it was just 'one other honor,' but to me, of course, without having had these honors, my friends down in Western Kentucky don't know whether I have been elected President of the American Medical Association, of some great medical university, or even of the United States (Laughter) It grieved my best friends to think that I had been elected the President of some great medical university, or that I would have to leave Lexington as President of the College of Physicians I have tried to reassure them, so that if they get sick next year, they might come back to ask me about it

"I have been thinking that, looking up at the altitude, at least, of these two former Presidents, Dr Meakins and Dr Miller, that if this thing keeps up very much longer going down like it is now, along about 1938 or 1939 you will be even below sea level as far as your President is concerned (Laughter)

"I couldn't possibly tell you, of course, really how great an honor this is to me It is something, of course, I never dreamed of in my life I just hope that I can do the best I can I know that it will be difficult for any president to steer this old Ship of State very far wrong because if we make any mistakes or if we even shy off the course a little, we have a pilot on board all the time who will see to it that we don't go too near the rocks I refer to Mr Loveland, our Executive Secretary

"I hope that with the cooperation of the members of the Society, which I know I will get, and the help of the Board of Governors and the advice of the Board of Regents, I will be able to carry on I know that we have big things before us next year The College is beginning to stand for more and more every year, it is becoming recognized more and more, and I cannot tell you how much I am honored by your electing me to this office I thank you very much" (Applause)

Dr William Gerry Morgan, Secretary-General "Dr Miller, on behalf of the College, I have the privilege of presenting to you this token of our appreciation of your splendid accomplishments during your year as President" (Dr Morgan presents the retiring President with an official gavel, appropriately engraved)

Dr Miller "Mr Secretary-General, Mr President, Fellows of the College it is a great pleasure to accept this symbol which is a symbol of an honor which has been conferred and which ever will be a memory of the great pleasure which I have had and which I have much enjoyed I thank you again" (Applause)

President Bradley called upon Dr Pottenger, a member of the Nominating Committee in the absence of the Chairman of that committee, Dr Sydney R Miller, for presentation of nominees for Officers, Regents and Governors, whereupon Dr Pottenger presented the following nominations The nominations for the elective offices had been published in the ANNALS OF INTERNAL MEDICINE, official journal of the College, more than thirty days preceding, in accordance with the By-Laws

President-Elect
First Vice-President
Second Vice-President
Third Vice-President

James H Means Boston, Mass
 O H Perry Pepper, Philadelphia, Pa
 David P Barr St Louis, Mo
 Walter L Bierring, Des Moines, Iowa

BOARD OF REGENTS

Term Expiring 1939

James D Bruce, Ann Arbor, Mich
 Egerton L Crispin, Los Angeles, Calif
 James Alex Miller, New York, N Y
 Francis M Pottenger, Monrovia, Calif
 Luther F Warren, Brooklyn, N Y

Term Expiring 1938

Robert A Cooke, New York, N Y (filling vacancy of the late Charles G Jennings)
 Hugh J Morgan, Nashville, Tenn (filling unexpired term of James H Means)

BOARD OF GOVERNORS

Term Expiring 1939

Oliver C Melson, Little Rock, ARKANSAS
 Ernest H Falconer, San Francisco, CALIFORNIA (Northern)
 Fred M Smith, Iowa City, IOWA
 Joseph E Knighton, Shreveport, LOUISIANA
 Henry R Carstens, Detroit, MICHIGAN
 Edward L Tuohy, Duluth, MINNESOTA
 A Comingo Griffith, Kansas City, MISSOURI
 Robert B Kerr, Manchester, NEW HAMPSHIRE
 Clarence L Andrews, Atlantic City, NEW JERSEY
 Charles H Cocke, Asheville, NORTH CAROLINA
 Julius O Arnson, Bismarck, NORTH DAKOTA
 Alex M Burgess, Providence, RHODE ISLAND
 Kenneth M Lynch, Charleston, SOUTH CAROLINA
 Paul K French, Burlington, VERMONT
 J Morrison Hutcheson, Richmond, VIRGINIA
 Charles E Watts, Seattle, WASHINGTON
 Walter E Vest, Huntington, WEST VIRGINIA
 D Sclater Lewis, Montreal, QUEBEC

Term Expiring 1937

Walter W Palmer, New York, NEW YORK (Eastern) (To fill unexpired term of Robert A Cooke)

Upon motion by Dr Meakins, seconded by Dr Musser and unanimously carried, the nominees presented by the Committee were regularly elected

President Bradley at this point expressed his appreciation of the manner in which Dr James Alex Miller had conducted the office as President during the past year, the way the College had been run and the kindness of the retiring President for his advice Dr Bradley expressed his keen approval of the plan of having a man serve one year as President-Elect, so that he may become more familiar with the needs of the College and the means of accomplishing those needs before he is inducted to the presidency He asked for suggestions from members at large, from the Governors, the Regents and other Officers, during the year

On motion by Dr Pincoffs, seconded by several and unanimously adopted by a standing vote, it was

RESOLVED, that the American College of Physicians express its deep appreciation to all local agencies, including the Wayne County Medical Society, local committees, the local profession, the Convention Bureau, the Book-Cadillac Hotel, the committees at Ann Arbor

and the University of Michigan for their aid and cooperation in the conduct of its Twentieth Annual Session

Adjournment

Attest E R Loveland,
Executive Secretary

MINUTES OF THE BOARD OF GOVERNORS

DETROIT, MICH

March 2, 1936

The first meeting of the Board of Governors of the American College of Physicians, held in connection with the Twentieth Annual Session, Detroit, Mich., was called to order at 5 25 p m, March 2, 1936, at the Book-Cadillac Hotel

In the temporary absence of the Chairman, Dr Charles H Cocke, Dr C W Dowden acted as Chairman pro tem The Executive Secretary called the roll, with the following present Dr Oliver C Melson, Dr Tom Bentley Throckmorton, Dr Joseph E Knighton, Dr James D Bruce, Dr Edward L Tuohy, Dr A Comingo Griffith, Dr Clarence L Andrews, Dr Julius O Arnson, Dr Alexander M Burgess, Dr J Morrison Hutcheson, Dr Charles E Watts, Dr Walter E Vest (representing Dr John N Simpson), Dr D Sclater Lewis, Dr Fred W Wilkerson, Dr Turner Z Cason, Dr Glenville Giddings, Dr C W Dowden, Dr Edwin H Gehring, Dr Louis H Fligman, Dr Robert A Cooke, Dr A B Brower, Dr T Homer Coffen, Dr Charles T Stone, Dr Ramon M Suarez, Dr James F Churchill, Dr Gerald B Webb, Dr Wallace M Yater, Dr Ernest E Laubaugh, Dr Cecil Jack (representing Dr Samuel E Munson), Dr Robert M Moore, Dr Thomas Tallman Holt, Dr Allen A Jones, Dr Leila Andrews (representing Dr Leander A Riely), and Dr Louis E Viko

Mr Loveland then read abstracted Minutes of the last meeting of the Board of Governors, which, upon resolution, were approved as read

Dr Walter L Bierring, Chairman of the Committee on the Certification of Internists (American Board of Internal Medicine) distributed copies of the articles of incorporation, the Constitution and By-Laws of the proposed American Board of Internal Medicine, and discussed at length the proposed organization of this board The details of the discussion are not repeated here, since they are duplicated in the Minutes of the Board of Regents

Dr Dowden called upon the Executive Secretary to present communications Aside from those from Governors who were unable to be present, Mr Loveland read ore from Dr Adolph Sachs, Governor for Nebraska, in which Dr Sachs suggested the desirability of changing the method of electing Governors The present By-Laws provide that a Nominating Committee appointed by the President shall, after consultation with members in the various States to be represented, prepare a slate of nominees for the Board of Governors Dr Sachs' recommendation was that Governors shall be elected by their local constituents

On motion by Dr Vest, seconded by Dr Giddings and regularly carried, it was

RESOLVED, that the Chairman shall appoint a Committee to investigate the proposal of Dr Sachs concerning the election of Governors and report back at the next meeting of the Board

Dr Dowden requested from the Executive Secretary a report on the elections to Fellowship and Associateship that had been made March first by the Board of Regents Mr Loveland reported that the list of elections had been posted on the Bulletin Board and that it included the full list of candidates elected both to Fellowship and to Associateship He offered to read the names to any who had not examined the list on the Bulletin Board

On motion by Dr Griffith, seconded by Dr Melson, and regularly carried, it was

RESOLVED, that the list of candidates, both for Fellowship and Associateship, as elected by the Board of Regents, be approved by the Board of Governors

The Executive Secretary, Mr Loveland, then reported upon the names of members who had been dropped from the roster for various reasons, including failure to take up membership within one year after election

At this point, Dr Charles H Cocke, Chairman of the Board of Governors assumed the Chair

Mr Loveland proceeded with his report, distributing to members a list of those Fellows and Associates from each State who were subject to being dropped because of more than two years' delinquency He also distributed an outline of the Associates elected at the 1931 Session whose names were being dropped for failure to qualify for Fellowship The Governors were asked to take the lists with them for future reference Mr Loveland pointed out that out of a membership of something over 3300 only 16 were dropped for delinquency, a very gratifying record Members of the Board of Governors were requested to make any suggestions concerning any names on the list, with the understanding that the Board of Regents would be glad to do anything reasonable if any mistakes had been made in dropping any of the members

Dr Cocke, as Chairman, thanked the Board cordially for their cooperation and for the very excellent attendance at this meeting, for the faithfulness with which they have done their work, and particularly for their care in responding to his various communications Dr Cocke reported that since the last meeting, the College had lost through death one Master, 32 Fellows and 6 Associates He also read the list of new Life Members added since January 1, 1936, including the following

Lewis Beals Bates, Ancon, C Z
Casper H Benson, Columbus, Ohio
Donald Gregg, Wellesley, Mass
James Rae Arneill, Denver, Colo
Thomas Fitz-Hugh, Jr, Philadelphia, Pa
C Charles Burlingame, Hartford, Conn
Noble Wiley Jones, Portland, Ore
Cecil M Jack, Decatur, Ill
Anna Weld, Rockford, Ill
Roy M Van Wart, Descanso, Calif (formerly of New Orleans)
Estes Nichols, Portland, Maine
William Henry Watters, Coconut Grove, Miami, Fla

Dr Cason, Governor for Florida, presented the matter of the time of the Annual Meeting He had been requested by several of the members in Florida to present a resolution asking for the postponement in the date of the Annual Meetings to a later time in the year Dr Cason had had communications from practically every member in Florida Some of them were unable to come because of the press of work, this being the busiest time of their season Furthermore, the character of the winter in the North in March was such as not to attract members from the warmer climates

Chairman Cocke explained that the date of the meeting is usually set by the local committee on arrangements in accordance with the necessities of their local conditions, schools, hospitals, etc He offered to entertain a motion, however, for presentation to the Board of Regents

On motion by Dr Cason, seconded by Dr Churchill, and regularly carried, it was

RESOLVED, that the Board of Governors recommend to the Board of Regents and such other Officers as may be concerned in the selection of the time for the Annual Meeting to hold future Annual Sessions at as late a date in April as consistent with the convenience of those in the city in which the meeting will be held

At this point Chairman Cocke brought up the question of alternates for members of the

Board of Governors who may be unable to be present at the annual meetings. The By-Laws make no provisions. The matter had already been brought to the attention of the Board of Regents on the previous day, and that Board had given authority to the Board of Governors, as they see fit, to accept the proxies of absent Governors who were unable to attend this particular Session, and to accept their substitutes to act in their full stead and to enjoy all their full rights under the Constitution. For this reason, Dr Walter E Vest, of West Virginia, was acting in the stead of Dr John N Simpson, Dr Cecil Jack, from Southern Illinois, was acting in the stead of Dr Samuel E Munson, and Dr Leila Andrews, of Oklahoma, was acting in the stead of Dr Leander A Riely.

On motion by Dr Dowden, seconded by Dr Cason, and regularly carried, the seating of the above alternates was approved.

On motion by Dr Griffith, seconded by Dr Giddings, and regularly carried, it was

RESOLVED, that the Board of Governors suggest to the Board of Regents the desirability of having the By-Laws amended to provide for the appointment of alternates for Governors who cannot attend the Annual Sessions.

Chairman Cocke then read a communication from Dr Henry M Thomas, Jr, Governor for Maryland, discussing the ultimate future of the College, and suggesting ways and means of approaching the chiefs of various important medical services concerning promising younger members of their staffs for Associateship.

Chairman Cocke pointed out that as soon as the American Board of Internal Medicine begins to operate, there may be certain changes necessary in the way candidates may become Fellows of the College. At present, except in very exceptional cases, new candidates must be presented first for Associateship. After the new Board is operating and a physician is certified as an internist by that Board, it will form the ground work or the foundation or the presumption of his eligibility for admission to this College, although there will be several other requirements.

Chairman Cocke asked for suggestions or ideas which he might transmit to the Board of Regents for their consideration.

Chairman Cocke proceeded to the matter of the reinstatement of old members, reporting upon two cases that had been liberally discussed by the Board of Regents the day before. If a man voluntarily resigns and is out of the College for a given period of time, it matters not whether it is a year or ten years, the Regents are disposed to require him to come back either through the regular channel of reelection or on the recommendation of the Governor for his district and the payment of all past dues. Members having voluntarily eliminated themselves by resignation do so on their own responsibility, and the College should not waive their requirements and allow a man the privilege of resigning and coming back at will. Such action would create a hopeless situation with men dropping and taking up their memberships constantly.

Dr Holt, Governor for Kansas, inquired concerning the effect of new changes that would be brought about by the operation of the American Board of Internal Medicine.

Chairman Cocke informed the Board that until the Constitution and By-Laws have been amended candidates will continue to come in under the present arrangement. It is quite certain, however, that amendments will be adopted as soon as the Board is ready to operate, and that thereafter new candidates will be subject to the new requirements.

Dr Burgess, Governor for Rhode Island, wished further discussion of the matter of reinstatement of members, presenting an illustrative case of a member stricken with pulmonary tuberculosis, or some other illness, making it necessary for him to retire from active membership in his societies. Such a man might later recover and desire to be reinstated.

Chairman Cocke replied that there was no need for such a man resigning, that the By-Laws provide that in the case of protracted illness and retirement from practice, a member is entitled to appeal to the Board of Regents for a waiver of his dues during such period. The Board of Regents, in accordance with the By-Laws, are considerate in such cases and, hence, no member needs to sacrifice his fellowship in the College because of his health. Upon a member's recovery and resumption of practice, his status changes to that of a paying

member, and in the meantime there is no necessity for reinstatement because he has remained a member all the time

Dr Moore, Governor for Indiana, reported on College membership in his State. In that State it has appeared difficult to procure men who are doing wholly Internal Medicine in any given smaller city. Many of the men in these cities who would be interested in the College, however, do restrict their work to 90 per cent or 95 per cent Internal Medicine. However, some of these are doing, to some degree, minor surgery and handling an occasional obstetrical case. Many of these men are interested in College membership, though the question has existed as to whether they are qualified under the circumstances.

Chairman Cocke suggested to Governor Moore that such men might properly be proposed for an Associateship. Candidates limiting their work almost wholly to Internal Medicine may be considered eligible for Associateship, with the understanding that before they come up for Fellowship they will probably be able to limit their work wholly.

Chairman Cocke then informed the Board of Governors concerning the details of the discussion in the Board of Regents concerning the procuring of a College Headquarters or permanent home. Quoting from his remarks: "The headquarters is located in a singularly small and inadequate suite of offices at 36th and Walnut Streets in Philadelphia. During the incumbency of Mr Loveland as Executive Secretary, the funds of the College have increased remarkably, namely, from approximately \$9,000 to \$158,000. It has been the thought of many of the Regents that since this fund has been raised without specific, definite, planned ideas for its distribution, or its use, although the College has used a certain amount for awards, for scholarships and that sort of thing, and while the College will continue to foster those projects, the time has arisen when the College must have more adequate, better and larger facilities, through the building or acquisition of a suitable home. Those who were present at the Regents-Governors Banquet last evening, March first, heard the discussion presented so well by Dr Alfred Stengel, Chairman of the Temporary Committee appointed to look into the feasibility of this project. I would be very happy to have any reaction or any remarks from any Governor present as to his feeling or thoughts of his constituents toward this possibility. Of course, a natural corollary of that would be that there would be some reduction either of the dues, or, more particularly, of the initiation fee once a permanent home has been acquired."

Dr Yater, Governor for the District of Columbia: "Mr Chairman, certainly there is no question as to the advisability or the necessity of such a permanent headquarters. It is perfectly ridiculous that such an organization as this should not have had one long since. Furthermore, with all the troubles brewing in our country at the present time and the possibilities of inflation, and what not, if we wait, say a year or so, to feel out the consensus of opinion of the majority of our members, we shall be losing very valuable time and money, because a year from now very likely the property which we can now obtain for a certain figure will probably cost much more and construction will be more expensive. This would seem to me also to be a very important consideration in the investment of our funds. In order to bring the matter to a point of discussion, I would move, Mr Chairman, that the Board of Governors shall express to the Board of Regents their approval of the project for the acquisition of a permanent College home and headquarters, and, further, that the Board of Regents proceed immediately on the project."

The motion was seconded by Dr Griffith, Governor for Missouri.

Dr Bruce, Governor for Michigan: "I can't resist the temptation to tell you all how gratified I have been personally and how gratified the members of Michigan have been with the progress of the College, and I am perfectly sure that I am expressing their wishes in supporting the motion that has been made. They will be very happy if this can be carried through."

Dr Tuohy, Governor for Minnesota: "I am glad to voice the opposition and to elaborate on what I have already said. I think it is quite obvious that you are going to have this building, but I shall appreciate, nevertheless, if you will bear patiently with me for a moment while I attempt to clarify my position. I believe the American College of Surgeons has

added nothing to the prestige of that organization, or to the advancement of the purposes for which they were originally established, by the acquirement of their home. I want to clarify the matter as to the centralization in Philadelphia. I think the advisability of that has been well proved by the success that has come to the College since the work was centralized, and so I think there is, in fact, no argument pertaining to that feature. Philadelphia is a happy choice, both from the standpoint of traditions of medicine and the first hospital and the first medical school established in the United States. If the College Headquarters were developed in Washington, near the Surgeon General's Library, I think the advantages would be of little moment in comparison to the equal advantages that exist in Philadelphia."

Dr Tuohy proceeded to ask for a consideration purely on a business basis, and pointed out that the College funds could be invested in other than United States securities, if inflation is threatened. He recommended careful consideration of renting more space in Philadelphia as a comparison with the cost of maintaining a College Headquarters. He questioned whether a College home would be considered by the members at large of any value. He recommended various methods of extending the sphere of influence in the College into various sections of our country, including regional convocations with the purpose of instilling better Internal Medicine into the various States and Provinces. He further pointed out that the Royal College of Physicians has given little attention to its housing. He urged no hasty action until the matter had been duly considered.

Dr Holt, Governor for Kansas, also spoke to the question, and Dr Cason, Governor for Florida, insisted on some word from the Executive Secretary from the standpoint of a business man who may thoroughly understand the facts of the case, because of his closeness to the College.

Chairman Cocke replied that the progress thus far had been carried on not only with the advice and cooperation, but with a very active interest of the Executive Secretary, but that the Executive Secretary had expressed a preference not to enter too actively in the discussion of the matter. However, he called upon Mr Loveland to make some remarks to the inquiries.

Mr Loveland pointed out, first, that the matter of the College Headquarters is one to be settled by the College. A committee had been formed which had called upon the Executive Secretary to determine certain information and to make certain surveys, report on which had been presented by Dr Stengel. He said he was favorable to the project, second, the College by conservative operation and care has accumulated a considerable surplus, which is likely to be dissipated with an increasing interest in other projects and probably through changing personnel on the various Boards. The By-Laws provide for a certain amount of change in members of the Boards, and without disparaging the good intent of any one, the investment of a certain part of the surplus in some worthy problem, such as an appropriate and dignified home for the College would be a safeguard. However, the chief consideration was the actual need of larger and more adequate quarters. Many members of the College visit the College Offices every year and frequently express disappointment in the rather small and inadequate quarters. The efficiency of the College work is somewhat hampered by inadequate facilities. He said he would not recommend an extravagant building, but something fairly modest, of attractive architecture and of reasonable proportions for present and future work of the College. In his opinion a permanent headquarters would contribute toward stability. These surplus funds might readily be used, if not for a College Headquarters, for other purposes that may be far less enduring. Adequate quarters would make it possible for members of the College to come to Philadelphia and use them for their headquarters, where mail could be sent, consultations held, and so on. The College, further, could operate better with its members in arranging programs to see what is being done medically in Philadelphia, or for postgraduate study. The headquarters might also be used for the giving of examinations by the American Board of Internal Medicine, after its formation. It is also possible that some other medical group or groups might use, on rental from the College, any excess space available for their own offices.

Dr Griffith, Governor for Missouri: "I want to go on record as saying that I am for

this proposal all the way through I do not think the American College of Surgeons and the American College of Physicians should be compared. One is a huge organization with many members and different branches all over the country. Ours is a real fellowship organization. We have a smaller, more limited number of members. I think we are an organization that should have a permanent home, a place to which we can point with pride. I am not in favor of Washington. That location would be all right if we were a larger political organization and wanted to get something out of the Government. As to inflation, whether we have stocks or bonds, we are drawing a certain interest from our money. The dollar is now worth only fifty-nine cents, and if we have further inflation, no one knows what its worth will be. If we have real property, we shall have something tangible, and the value will be there."

Dr. Suarez, Governor for Puerto Rico: "This is the first meeting of the Board of Governors that I have attended, and I have been most favorably impressed by the things I have heard. It took me six days to get to this meeting, and I cannot resist the temptation to say at least a few words about the building of a permanent home for the College. I have been President of the Puerto Rico Medical Society for three years, and during my incumbency, a beautiful home for the medical profession of the Island has been built. We are proud of it and we think it is one of the best things we could have done for the medical profession there. I frankly and firmly believe that the construction of a permanent home for the American College of Physicians would be a most definite sign of permanency and stability, and I see no reason why, since we have progressed so wonderfully since our headquarters were established in Philadelphia, the new building shouldn't be constructed also in that City."

Dr. Giddings, Governor for Georgia: "It seems to me that it is practically essential for this College to have a headquarters. Certainly if this examination and certification of internists is passed and put into operation, the necessity of such a headquarters will be even greater. I rather feel that we not only should have a home, but that the place should be fireproof, and I rather question whether such a structure can be erected for the sum that has been suggested."

Dr. Moore, Governor for Indiana: "I want to be on record as for this project. I feel favorable toward establishing a permanent home. As to other projects of the College, I am well acquainted with fellowships. I have observed many fellowships established to help students through school. It doesn't make a bit of difference whether it is a fellowship from the American College of Physicians or some other organization. Most of the money spent on these fellowships is soon gone and forever forgotten. If we have something substantial to which we can point, I think it will bring prestige to our organization, as it should. It doesn't make any difference whether it is your own office or the headquarters of your organization. If you have a poor office, it doesn't impress your visitors favorably. An organization of our standing and our honor, I think, can have nothing but the best."

Chairman Cocke put the motion to a vote, whereupon the resolution was unanimously adopted.

RESOLVED, that the Board of Governors shall express to the Board of Regents their approval of the project for the acquisition of a permanent College home and headquarters, and, further, that the Board of Regents proceed immediately on the project.

At this point, Chairman Cocke introduced the President of the College, Dr. James Alex. Miller. (Applause)

President Miller: "It is particularly a pleasure to be here and to get the reaction of the Board of Governors on this conception which has arisen in the Board of Regents, and I can tell you that your reaction taken this afternoon will have very great weight in determining the action of the College through the Board of Regents, where, of course, the responsibility lies. I also want to say that at our meeting last night, it was a great pleasure to us of the Board of Regents to be your hosts. That dinner was not a College affair, but was a spontaneous and personal invitation on the part of the members of the Board of Regents to the members of the Board of Governors, expressing the personal anxiety of the former to get

closer to the Governors That was the basis on which that meeting was held, and which I hope will be a precedent for similar meetings I also want to say that during this last year, over which it has been my privilege to preside as your President, I have been more and more impressed with the importance of the Board of Governors individually and collectively in the affairs of this College Of course, we have our Constitution and By-Laws, certain prerogatives, certain details and privileges are assigned to the Board of Regents and others to the Board of Governors, but we are all cognizant that it is the personnel of the College which counts, and it is there that the Board of Governors must take the initiative I feel so strongly about this that I have made it the practice during the last two or three years not to exercise as Regent my prerogative to certify or to endorse candidates I think that under certain exceptional circumstances, perhaps, it is wise to allow a Regent to endorse a candidate, but I have made it an invariable rule when proposals have been sent to me to refer them to the Governor of my district, in order that they may go through the regular channels of the Board of Governors, because I believe the responsibilities should rest with them, and I believe it is up to you, gentlemen, to exercise as you have in the past, but even increasingly in the future, a good deal more of a sense of responsibility in passing upon the credentials of candidates whose proposals you pass to the Committee on Credentials It is not fair or right to send a doubtful candidate's proposal to the Credentials Committee, you usually have available first-hand information, whereas that Committee does not, and if they do not receive it, they cannot act in the best interests of the College

"I also think that you should insist more and more upon discretion on the part of Fellows who present candidates to be endorsed by you We must have greater local autonomy, or at least a greater local sense of responsibility toward the problems of the College

"I, too, feel as you, gentlemen, have expressed it, that we will go far, if we have our permanent home, toward increasing the feeling of pride and stability in our organization, which I think is extremely important An even more important step is that which we are making on the question of the certification of internists, which, when it is consummated, will make it quite possible for us to use that examination instead of the preliminary stage of Associateship That is not yet an assured fact, but is being considered in that connection You should understand that it is not the idea of the present Board of Regents that this certification will in any sense qualify an individual for Fellowship It will simply give him the basic minimum requirement, and in the future, I hope, no one who is not certified as an internist will be even considered by our Credentials Committee After that, we can add any particular requirement and essentials that we think wise I feel sure we are just ready for a move forward for this organization which is going to make it a great power, not only from the standpoint of the standards of practice, but also in the standards of qualification for certain types of practitioners, specialists, if you want to call them such I hope we shall also have an opportunity to exercise great influence on ethical standards, which are tremendously necessary I think we may be very proud of the leading part that the College has taken in this matter Thank you very much for the privilege of speaking to you" (Applause)

On motion by Dr Griffith, seconded by Dr Yater, and adopted by a unanimous rising vote, it was

RESOLVED, that the Board of Governors express to the members of the Board of Regents their keen appreciation and thanks for the Dinner tendered them on March 1

Adjournment

Attest E R LOVELAND,
Executive Secretary

MINUTES OF THE BOARD OF GOVERNORS

DETROIT, MICH

March 5, 1936

The second meeting of the Board of Governors of the American College of Physicians, during the Twentieth Annual Session, was held Thursday, March 5, at the Book-Cadillac Hotel, with Dr Charles H Cocke, Chairman, presiding, and with the following present Dr Oliver C Melson, Dr Tom Bentley Throckmorton, Dr Joseph E Knighton, Dr James D Bruce, Dr Edward L Tuohy, Dr A Comingo Griffith, Dr Clarence L Andrews, Dr Charles H Cocke, Dr Alexander M Burgess, Dr J Morrison Hutcheson, Dr Walter E Vest (representing Dr John N Simpson), Dr D Sclater Lewis, Dr Fred W Wilkerson, Dr Turner Z Cason, Dr Glenville Giddings, Dr C W Dowden, Dr Edwin W Gehring, Dr G W F Rembert, Dr Louis H Fligman, Dr A B Brower, Dr T Homer Coffen, Dr Charles T Stone, Dr James F Churchill, Dr Gerald B Webb, Dr Henry F Stoll, Dr Wallace M Yater, Dr Ernest E Laubaugh, Dr Cecil Jack (representing Dr Samuel E Munson), Dr Robert M Moore, Dr Leila Andrews (representing Dr Leander A Riely), Dr Louis E Viko and Dr Jabez Elliott, and E R Loveland, Executive Secretary, acting as secretary of the meeting

By resolution, the reading of the Minutes of the previous meeting was dispensed with

Chairman Cocke reported to the Board upon matters he had been instructed to refer to the Board at a previous meeting

(1) The resolution urging the Board of Regents to proceed toward the acquisition of a College Headquarters was favorably received and spread upon their Minutes

A new committee was appointed by the President to take the matter in hand, with instructions to bring in definite and concrete specifications as to location, type of building, etc, at the next meeting

(2) The resolution containing recommendation for amendments to the By-Laws providing for appointment of alternates for Governors who cannot attend the Annual Sessions was approved, and the Committee on Constitution and By-Laws instructed to draw up proper amendments

(3) The resolution requesting a later date for the Annual Sessions was received and given due consideration, with the result that the 1937 meeting will be held later in the year than customary

At this point, Chairman Cocke called upon a special committee previously appointed to consider the suggestions of Dr Adolph Sachs, Governor for Nebraska, for a new method for election of Governors The following report was received

"The Committee appointed by you to consider the suggestions made by Dr Adolph Sachs, Governor for Nebraska, namely, 'that in the future the Governor for each State shall be elected by the Fellows in his respective State or district,' met Wednesday afternoon, March 4, 1936, and, after due deliberation, unanimously recommends that there be no change in the present method as provided in the By-Laws, for the following reasons

"First, under the present efficient method carried out under the By-Laws, the College has advanced and thrived without any type of dissension

"Second, your Committee is quite fearful that if the election of Governors be left to the decision of Fellows in the respective States, politics might readily enter

"Respectfully submitted,

C L ANDREWS,

F W WILKERSON,

A C GRIFFITH, *Chairman*"

On motion by Dr Knighton, seconded by Dr Yater, and regularly carried, it was RESOLVED, that the Board of Governors adopt the above report

Chairman Cocke reported that while the final amendment would specify the method of appointing alternates, it was his understanding that the power of appointing an alternate would be vested in the local Governor, who should certify to the Executive Secretary the appointment of his alternate, and should give a letter of appointment to the alternate himself

The Executive Secretary, Mr Loveland, distributed copies of the financial report of the College for 1936 He reminded the Governors that while the Board of Regents is responsible for the business operation of the College, it is desired to keep the Governors also informed He reminded them that the accounts of the College are audited each year by a certified public accountant He reviewed the various parts of the report, summarized the operating statements and explained the General and Endowment Funds The financial reports have been published in connection with the Minutes of the Board of Regents, and are not here repeated There was general discussion about the various statements, and a keen interest displayed by members of the Board

Dr Throckmorton, Governor for Iowa, called attention of the Board of Governors to the income from the annual exhibits, as shown in the statement He stated that that was one of the first things which struck his attention, because of his own experience with exhibit work in his State society and in some national organizations He pointed out that the success of these exhibits represents an unusual amount of work carried on by the Executive Offices, and it should be deeply appreciated by the College He added, "I know from personal experience that it takes a lot of good hard work not only to get exhibitors, but after having gotten them to keep them satisfied and to keep them coming, and for that reason I personally want to compliment the Executive Secretary and his staff upon that unusual work which they have done in this particular line It shows in the income that it is a mighty fine thing for the College I would call your attention to the fact that this activity accounts for a considerable part of the surplus which may be used for the acquiring of a College home and other activities I want to say that this surplus came largely from the sweat of the brows of the Executive Secretary, the Finance Committee and the Regents, and there is nothing unworthy about it at all"

Chairman Cocke pointed out that the commercial exhibits before the College meetings are carefully censored, and an earnest effort is made to admit only the most ethical and reliable products

Dr Vest reported that his examination of the exhibits had shown that nothing in the exhibit was worthy of criticism in any way They were all proper exhibits

The Executive Secretary then reported upon the publication, during the autumn of 1935, of a new Directory of the College He called attention to the revised arrangement of data, and expressed the hope that the usefulness of the Directory would be greatly extended Mr Loveland further reported on the new Life Members of the College, totalling now 61 in all, he reported on the elections to Fellowship and Associateship and gave the membership statistics By resolution, the report of the Executive Secretary was accepted

The Executive Secretary presented for the advice of the Board of Governors the problem of whether or not there should be published in the Directory the names of all Associates as well as the Fellows, as done at the present time As a matter of fact, Fellows and Masters only are "members" in the true sense of the word, since Associates do not have the power to vote, nor is the Associate roster a permanent one Associates of the College in general may be divided into three groups (a) those who first entered as members of the American Congress on Internal Medicine and were automatically given the status of Associates when the said Congress was merged with the College in 1926, (b) men elected to Associateship after meeting definite requirements for the same between 1926 and 1929, (c) Associates elected since 1929 who are under obligation to qualify for Fellowship within a maximum period of five years from election to Associateship The first two groups may remain Associates indefinitely, because the amendment to the By-Laws requiring qualification

for Fellowship by Associates only began to apply in 1929. Suggestions had been received in the College office that possibly the official Directory of the College, upon which members of the College are judged, should include only full-fledged Fellows.

Chairman Cocke requested a discussion of the matter.

Dr. Bruce, Governor for Michigan, after discussing the matter, summarized his opinions by saying that he felt we are perfectly able to vouch for all the Associates who have been elected since 1929, because they were compelled to meet certain definite requirements, and unless they succeed in qualifying for Fellowship, their names automatically will be dropped. For the earlier group of Associates who were brought into the College automatically, he felt some provision should be made so that they could be distinguished from the rest of the Associates.

On inquiry from Dr. Dowden, Governor for Kentucky, it was brought out that the American Medical Association in its Directory does not recognize as members of the College others than Masters and Fellows. Dr. Dowden expressed the opinion that Associates might be omitted from the Directory, so that confusion of Associates as full-fledged members might be obviated.

Dr. Knighton, Governor for Louisiana, expressed his gratitude for having the various classes of Associates clearly defined. He continued to report upon a sectional meeting of the Fellows and Associates of the College in the form of a combined clinical and social meeting in Shreveport during January, 1936. The membership especially represented was that of northern Louisiana. Dr. Knighton reported a very successful meeting with full attendance, lacking two, in that entire territory, and with additional meetings planned for the future.

Returning to the matter of the College Directory, Governor Griffith suggested that Associates of the College granted by virtue of membership in the old American Congress on Internal Medicine should be published separately, or under special designation.

Dr. Jabez H. Elliott, Governor for Ontario, concurred in this suggestion. Dr. Elliott said that it should be a question for discussion whether the College should carry the Associates in the Directory at all, because of the confusion in the minds of certain people as to whether or not they are full members of the College. However, if the Associates shall be published, then those who were admitted previous to the establishment of definite admission requirements should be set apart.

Chairman Cocke pointed out the condition should be corrected in the next Directory, but inasmuch as the next Directory will not be published until 1937, the intervening time might be used for more mature thought and for definite action at the next meeting. Dr. Cocke suggested that perhaps one of the means of handling this situation would be to have a full official Fellowship Directory of the College and to issue a supplementary Directory of Associates. The official Fellowship Directory would be the one distributed to libraries, medical schools and other official institutions.

Dr. Vest suggested that in our Directory we should publish only the Fellows and a list of "eligibles." This eligible list would include only those who are eligible for advancement to Fellowship, and would eliminate the names of all those who have not met the preliminary requirements for Fellowship.

President Bradley, at the request of Dr. Churchill, explained that the American Congress on Internal Medicine and the American College of Physicians were founded as two separate organizations. The first essential to be a member of the American Congress on Internal Medicine was merely a desire to attend its meetings and to pay an admission fee of \$5.00. There were always requirements for admission to the College. However, the meetings of the College and Congress were held together, and members of the College were recruited more or less from members of the Congress. When the Congress was discontinued, its members were accorded Associateship in the American College of Physicians.

Dr. Brower, Governor for Ohio, inquired how many such Associates still remain on the list and what is their average age. An examination of the list by the Executive Secretary

indicated there are 173, whose average age is 57 years. Ten of these are 65 years of age or older, and, therefore, on the dues-waived list. The balance pay the regular Associateship dues.

Dr Moore, Governor for Indiana, and Chairman Cocke both concurred in the opinion that this Directory is being used by hundreds of physicians who are not members and by hosts of physicians who do not attend the Sessions of the College. It is not infrequently that the Directory is used for reference for physicians to whom patients may be referred because of the removal of such patients from one part of the country to another, or because of travel. They expressed the opinion that the Directory should contain only the names of physicians whose credentials are of high grade.

Dr Andrews, Governor for New Jersey, expressed the opinion that the College is under some obligation to this earlier group of Associates, because of the original agreement to grant them Associateships.

Dr Hutcheson, Governor for Virginia, suggested that Fellows be given complete geographic and alphabetical listing, but Associates be listed alphabetically only in the back section of the Directory.

Dr Holt, Governor for Kansas, expressed the opinion that the obligation of the College to these early Associates is such that their regular listing should be maintained.

Dr Ernest B Bradley, President-Elect of the College at this juncture was called upon to address the Board of Governors briefly, asking them for their suggestions, aid and cooperation during the coming year, the term of his Presidency.

Chairman Cocke opened a discussion of regional or State meetings of members of the College. He expressed the opinion that the objects of these are (1) the establishment of greater coherence among the Fellows, (2) building up of more local pride in Fellowship, (3) dissemination of a better understanding of what the ideals and purposes of the College are, and (4) the furtherance of wider acquaintanceship and better fellowship among the members.

Dr Cocke reported that during the past year he had attended two of the State meetings, one in Kentucky and one in his own State of North Carolina. He had had reports from several Governors who had conducted such meetings in their territories. These meetings should be conducted by the Governor, and in some instances may be joint meetings among two or three neighboring States where the membership is smaller and the cities not too far removed from one another.

Dr Griffith, Governor for Missouri, announced that during the meeting of the American Medical Association in Kansas City during May some attempt will be made toward having a social meeting of members of the College from that community. He extended a cordial invitation to all members of the Board of Governors, Board of Regents and members of the College to be there.

Dr Yater, Governor for the District of Columbia, recommended that the College office should maintain up-to-date records about all of the members of the College, new honors, new positions, new publications, etc. He said there should be some one place in the country where internists shall have available a complete up-to-minute record of the medical histories of the outstanding men. Each year a form could be sent out by the Executive Secretary to all of the Associates and Fellows, probably more importantly to the Associates, asking them to put down changes in their status in their respective communities, new positions they are holding, outline of articles they have written, outline of papers they have delivered before national organizations, etc. This might also be quite a stimulus to Associates who must prepare their credentials for Fellowship by inquiring each year what they have accomplished during the preceding year. They will be reminded and given a stimulus toward better qualifying themselves for Fellowship.

On motion by Dr Yater, seconded by Dr Andrews, and regularly carried, it was

RESOLVED, that the Board of Governors suggest to the Board of Regents that each year the Executive Secretary send out appropriate questionnaires to obtain information as to the

status and work that members of the College have done during the preceding year, and that these records shall be kept on file in the headquarters office

On motion by Dr Giddings, seconded by Dr Yater, and regularly carried, it was

RESOLVED, that the Board of Governors draw up resolutions expressing its very deep sympathy for the family of Dr Charles G Jennings and also for the family of Dr Frederick Epplen (Secretary's note Dr Charles G Jennings, deceased, was General Chairman of the Twentieth Annual Session at Detroit, 1936, a Master of the College, and for many years Chairman of the Board of Governors, Dr Frederick Epplen, deceased, was for many years Governor for the State of Washington)

Dr Andrews, Governor for New Jersey, expressed his disappointment that the Daily Bulletin had been discontinued at the current Session. He expressed the opinion that many other members were likewise disappointed. It served as an aid in locating members of the College who were in attendance at the meeting and as a guide to the happenings of the current day.

The Executive Secretary, Mr Loveland, explained that the Daily Bulletin had been discontinued primarily because of the expense of publication and the amount of work entailed. The Daily Bulletin had to be printed at night. The burden fell upon the Executive Secretary's office because there was no one else available to edit the Bulletin. It had been initiated unofficially by him a few years back for the sake of aiding the exhibitors whose daily write-ups appeared therein, in addition to the outline of committee meetings, registrations, etc. On one occasion he had sought the Editor of the ANNALS OF INTERNAL MEDICINE to act as Editor of the Daily Bulletin, but the Editor had not found it possible to take on this added duty. Exhibitors had expressed the opinion that the Daily Bulletin was of little or no value to them, provided the Executive Offices would furnish them with lists of the registration at the end of the meeting. There had been very few comments of the members indicating appreciation of the Bulletin, and, therefore, because of the cost and tremendous amount of work connected with its daily appearance, it had been discontinued. Mr Loveland, however, explained his willingness to place the matter before the Board of Regents and to continue its publication if so authorized.

Dr Churchill, Governor for southern California, reported that he too had heard many remarks expressing disappointment about the discontinuance of the Daily Bulletin at the Detroit meeting. He said that he himself had missed it because being one who has some difficulty in associating names and faces, the Bulletin has been a great aid in identifying those present.

Dr Cason, Governor for Florida, suggested that the College keep the situation in Havana, Cuba, open as a possibility for taking some of the men into the College membership. Some years ago the Board authorized him to keep the situation in mind, and he has continued his contacts, but conditions have been so chaotic that no steps have been taken.

Adjournment

Attest E R LOVELAND,
Executive Secretary

ANNALS OF INTERNAL MEDICINE

VOLUME 10

AUGUST, 1936

NUMBER 2

THE PRESENT STATUS OF THE TREATMENT OF PULMONARY TUBERCULOSIS*

By LAWRASON BROWN, M D , F A C P , *Saranac Lake, N Y*

THE marked decrease in the mortality of pulmonary tuberculosis is undoubtedly due to many causes. It is not, many hold, a true measure of the decrease of the morbidity of the disease. Pulmonary tuberculosis is still a very menacing cause of death to both sexes during the period of greatest bodily and mental activity. The keen desire for a cure for tuberculosis, a true *therapia magna sterilisans*, so widely spread at the beginning of the century, is now less evident. Some foundations and laboratories consider tuberculosis an unpromising field of endeavor and have left it largely to the clinicians and sanitarians, who have contributed much. Few will question that more efficient treatment is one of the causes of the decreased mortality. Such treatment acts in two ways: it frees the sputum of tubercle bacilli and aids the victims to arrest really and permanently their disease or to live long enough to die of other causes.

To assess the value of different methods of treatment in any chronic disease is far from simple. The faith of him who introduces a new measure is too often passed on to him who receives it. Several years ago I spoke to some members of this College of the influence of the mental aspects upon the results of the treatment of pulmonary tuberculosis. I attempted to show at that time what a powerful effect suggestion, applied consciously or unconsciously, played in the results of treatment. I think I recalled at that time the practice attributed to an acquaintance who, posing the tuberculin containing syringe, uttered just as he inserted the needle, the incantation, "This is the life giving fluid." Any patient to whom he had in the vernacular "sold the idea" of tuberculin responded no doubt as fully as those lulled to sleep with the words, "You are better in every way every day." Misery undoubtedly begets credulity. This is probably the explanation of why many measures for the relief of pulmonary tuberculosis are helpful in the hands that introduce them, failures in the hands of others.

We hear today on all sides how the treatment of pulmonary tuberculosis has been revolutionized since the introduction of collapse therapy. For

* Presented at the Detroit meeting of the American College of Physicians, March 6, 1936

the "far advanced" patient and for many of the progressively "moderately advanced" patients this is true. We all hail the advances made possible by the fundamental studies not only of the surgeons but also of the physicians Brauer, a physician of Marburg, and later of Hamburg, spread the idea of collapse treatment throughout Europe and even back to America after he had received the suggestion from an American surgeon. Forlanini, the father of pneumothorax, was a physician. If we really face the facts, none of us can today think of the treatment of pulmonary tuberculosis without having always before us this collapse treatment. Some of our surgical confreres almost scout the idea that pulmonary tuberculosis is anything else than a surgical disease. They would have us hurry most patients to the operating room for fear that the disease may progress too far for surgical relief. They even lead us to believe that at some stage every patient can be greatly helped by the needle or by the scalpel. After living with pulmonary tuberculosis for some 35 or 40 years I cannot accept such a statement without some reservations.

The majority of those familiar with pulmonary tuberculosis in all its stages do not hold that patients in the minimal stage require, by and large, any form of surgical treatment. Certainly the great majority have recovered without such interference, and the last word is chosen carefully. The records at the Trudeau Sanatorium reveal only 8 per cent of these "minimal" patients dead at the end of 15 years. Such patients rarely fall into the hands of the surgeons, and many surgeons are not familiar with the excellent results obtained in such patients. Indeed some surgeons speak as if patients in this early stage presented cavitation, which is entirely wrong, for cavitation places them immediately in the second or advanced group. I might go even further and state that few, very few, of these "minimal" patients, only those with definitely advancing disease after treatment by rest, exposure to fresh air, by feeding with good food, and by treatment of symptoms as they arise, require more than these simple measures. But to treat pulmonary tuberculosis successfully does necessitate familiarity with the use of these fundamental means and how to judge of their effects.

It is then extremely important to know the proper treatment of this early stage of pulmonary tuberculosis. As soon as it has been diagnosed and as soon as it is determined that the lesion is active, rigorous treatment should be instituted. Now this treatment, less empirical than it was some 35 years ago, still revolves about the triad of rest, food, and air. Experience accumulated as the years have rolled on, based upon the unfortunate outcome of the treatment of certain patients, has emphasized the fact that the knowledge of the proper use of these seemingly simple measures is not acquired in a single interview to such a degree as to lead to certain and ultimate recovery. To this end we must add to the triad the education of the patient. The fundamentals then of all successful therapy of early pulmonary tuberculosis consist of (1) rest in the beginning and properly regulated

exercise later, (2) good food, (3) fresh air, (4) and finally, to insure the permanency of the recovery, proper education of the patient

(1) Concerning rest Injury ever demands rest for repair Surely the reason for pain in the universe is not only to teach the uselessness of breaking the laws of nature but also to emphasize the value of rest Unfortunately pulmonary tuberculosis is only infrequently associated with pain and the ignorant have their fears quickly lulled into a false sense of security and of approaching well being Weakness, they argue, can be overcome by exercise Many, conscientiously and literally, have walked themselves into their graves For these reasons I invariably put all such "minimal" patients to bed for a period of at least six weeks I permit them to go to the bathroom and even certain of them to go to the table but never allow them to dress or to go up or down stairs I attempt to explain to them why the lung requires rest for recovery Later I get them out of bed very gradually, permitting them to begin exercise at the end of six weeks by walking one or two minutes twice a day, without dressing, and increasing the amount of walking by one or two minutes a day until they are walking 20 minutes twice a day Then if they have a flight of steps to navigate I start them on one step a day until they reach the bottom Not until then do they dress Following this they walk on the street at first for 10 minutes twice a day for a week, then for 20 minutes, for 30 minutes, for three-quarters of an hour and finally for an hour twice a day When they reach this stage they can seldom hurt themselves by walking on the level to which I have so far confined them The recollection of this slow progress has a very salutary effect upon their future actions My suggestion is that in proportion as you can give any organ functional rest so you can aid it to recover from tuberculosis

(2) Concerning food There has been abroad in the tuberculosis land an impression that if a little food was beneficial, an increase might be more quickly helpful This was no doubt the basis for the old saying at the Trudeau Sanatorium that a patient must eat once for himself, once for the germs, and once to gain weight You will recall that in the time of Laennec and Louis a reproach, thrown in the faces of those who advocated the early diagnosis of phthisis, was that such a diagnosis led but more surely to the grave This rebuke, uttered both in Europe and in America, had much truth in it About a decade later you will remember the London *Lancet* intimated that if Dr George Bodington continued to feed his patients such food as beefsteak he would lay himself open to prosecution for malpractice Now at this time early diagnosis of pulmonary tuberculosis was rarely made, and when made, could usually be confirmed from across the way Such emaciation demanded food in far larger quantities than is needed for the class of patients we are now discussing The amount of good food that has been wasted upon the early patients has been appalling and unfortunately upsetting The strict Gerson diet, so effective in some cases of cutaneous tuberculosis (especially lupus), is far less, if at all, helpful in pulmonary

tuberculosis For some years, in the hope of changing an exudative into a proliferative reaction, I have been using, with some encouragement, a diet high in vitamins C and D, restricting the intake of sodium chloride and giving dicalcium phosphate I would like to suggest that the least amount of food that any patient who is under weight can gain upon is the optimum diet for that patient

(3) Concerning fresh air Inflammation of the lungs, it was held years ago, demanded protection Pulmonary tuberculosis was associated with such inflammation and so required protection also Night air was bad Change in temperature was deleterious So the patient should never go out at night and the temperature of the house must be kept high and not vary Such views were as wrong as those of the *Lancet* on diet They were based on two erroneous principles first, that patients with pulmonary tuberculosis needed warm and equable climates, and second, that the only organ concerned in recovery was the lungs Today we know that fresh air affects the lungs no more, no less, than it does the knee The chief effect of aerotherapy is manifested through the skin, and a variation of 20 degrees during the 24 hours is highly desirable These early patients should have a room connected with a porch upon which the bed can be rolled If this cannot be had, there should be a bed on the porch and one in the room I am no advocate of sleeping out of doors for patients who spend hours in the open air every day During the cool and colder months I insist that the patient spend at least six or seven hours in the open, tempering the time to the vigor of the patient Such patients can recover in a room but the psychological stimulation, apart from any other factor, makes some hours on a porch most desirable I would suggest that recovery from pulmonary tuberculosis depends upon six or seven hours in the open, and on good ventilation during the remainder of the twenty-four

(4) Concerning education This should begin at the time of diagnosis Ignorance inflicts often severe and possibly fatal penalties Even when they pay a lesser price ignorance often issues to patients a pass to the surgeon whom we are now trying to avoid Further, a little knowledge is a dangerous thing, especially when passed on from one patient to whom it may apply to another to whom it may bring disaster Three months are necessary for the education of any patient The time you keep him in bed is your golden opportunity He is most anxious to learn how to avoid bed in the future Urge him to ask questions, have him write them down Treat him as an adult Give him answers for whys and wherefores Be frank but optimistic The value of a good nurse who is familiar with pulmonary tuberculosis is inestimable I would suggest that in any chronic disease like pulmonary tuberculosis the therapeutic triad will bring about arrest of the disease, but education alone will make it permanent

For patients in the minimal stage it is remarkable what these apparently simple measures, when intelligently applied, will accomplish I have already stated that among the patients discharged from the Trudeau Sanatorium

it has kept 92 per cent alive for at least 15 years. If there is any other form of treatment that produces better results I am unaware of it and am keenly desirous of hearing about it.

Furthermore, all patients with or without surgical interference, sooner or later, for a longer or shorter time, must follow such treatment. Hence the necessity for complete and accurate knowledge concerning it. Where these measures should be used is for most of these "minimal" patients of far less importance than the length of their application. The surgeons have stated that it requires little or no more time for a long than for a shorter incision to heal. Applying this to pulmonary tuberculosis I would like to emphasize that a small but definite lesion of pulmonary tuberculosis demands several years of treatment, possibly more or less modified, for a permanent arrest. Failure to recognize this and to pass it on to the patient is the most frequent cause of relapse among these early patients. Emphasize that while work may be resumed, arrest too often lingers. Tell him he may play and get well, or work and get well, but rarely can he work and play and get well.

When the patient has passed beyond this early stage the picture changes. The outlook is very different and much more serious, for the progress of the disease may now be difficult to check or such damage may already have taken place that any hope that a permanent arrest may follow the simple measures previously outlined has to be abandoned. However, granting the possibility of a successful result, so long a time is now required to bring about the desired recovery by simple means that for many it is an economic impossibility. Even for those with means the years of sacrifice of ambitions and of desires are too likely to be interspersed with periods of lapses from the straight and narrow path of tuberculosis rectitude which may lead the wanderer into the purgatory of relapse. This is the stage of disease for which surgical treatment is usually recommended and is often successful. However, not all "advanced" patients require this surgical interference but for some it must be considered immediately if their chances of arrest are not to be squandered in dangerous procrastination. I am inclined, even in the minimal group, when economic pressure is present, in the face of a continuously but slowly advancing lesion, to apply certain surgical measures. Artificial pneumothorax is, of course, included under this head.

To make myself clear, I include under the head of "advanced" patients all save those in the minimal stage. You will recall that patients in the minimal stage never have a cavity nor can the disease extend below the second rib on one side nor below the clavicles if bilateral. Of course a similar extent of disease in any area of the lung places the patient in the minimal group. In the "advanced" patients there are several conditions of paramount importance in regard to treatment. I refer first to the type of disease, proliferative or exudative, second, to the destruction of tissue, i.e., cavity, third, to the age of the patient, and fourth, to his race. The proliferative type may not force us into immediate action but the presence of an

exudative state indicates a more acute process, a more treacherous disease, that can pass at a bound from a temporizing condition into one that spells defeat or, unfortunately less often, almost as rapidly clear up. The presence of a cavity demands nice discrimination from the physician in charge of the patient. There are several important factors in this connection. First, the size of the cavity (the larger, the more serious), second, its location in regard to the pleura and fissures (the nearer, the less likely the efficacy of simple collapse), third, the condition of the wall of the cavity (absence of a wall under certain conditions is more favorable, the thicker the wall, usually the more serious is the condition), and fourth, the associated disease (the more advanced the more dangerous).

The age of the patient cannot be overlooked. Those in the "teen" ages require more careful watching, more active, more expeditious treatment. If, perchance, the patient be a girl, these requirements are emphasized. Recent studies with the roentgen-ray explain why some of these children are never seen to pass through a minimal stage of the disease. The lesion progresses under cover without exciting symptoms until such time as an acute cold or an hemoptysis draws attention to the lungs, when the disease is found to be already in an advanced stage. The only way to treat such patients is to discover them by routine tuberculin testing and roentgenography applied during their high school days. The resilience of youth favors recovery, its exhilaration lessens the chances of recovery. With increasing years relapse is said to be more frequent, recovery less pronounced, advance of the disease slower.

I have spoken of active expeditious treatment and by this I mean some form of collapse therapy. The most widely used is, of course, artificial pneumothorax. An efficient collapse by this treatment occurs in about 40 per cent of all suitable patients. About three-quarters of these achieve a permanent arrest of their disease. So of those selected for the induction of pneumothorax 30 per cent are arrested. The remaining 70 per cent should not be subjected to artificial pneumothorax for too long a time for unquestionably ineffective or contraselective pneumothorax is dangerous and may hasten the patient toward his death. Happily intrapleural pneumolysis has converted many cases of ineffective into effective instances of collapse, terminating in permanent arrest. Some have suggested that the benefits of artificial pneumothorax are bought with the price of some loss of lung function, more than is entailed in the natural cure, and while this may be so, the appalling death rate in those in whom artificial pneumothorax is tried unsuccessfully, fully justifies the procedure. It is questionable whether this form of collapse treatment shortens the time of curing but undoubtedly it does abbreviate the period of inactivity. While the number of patients suitable for artificial pneumothorax is considerable, the remainder, together with the failures, compose a large group. For these other methods of treatment must be sought.

The phrenic operation follows artificial pneumothorax closely in frequency of use. It has undoubtedly been used at times psychologically to offset the disappointment at failure of other methods. The number of these forlorn hopes is larger than some of us imagine. In carefully selected patients the results of cavity closure are encouraging. They are far better among the moderately advanced type than among the far advanced. (In my experience 62 per cent against 12 per cent.) A temporary phrenic operation removes some of the objections offered to the operation. I have been disappointed in the results obtained when I have employed it to bring about closure of a cavity in a lung partially collapsed by artificial pneumothorax. Combined with scalenotomy or followed by scalenotomy better results may be had in some few instances.

May I say a word about postural rest at this time. Many apparently believe that by placing the patient upon the diseased side the affected lung would suffer less. Many years ago we called attention to the fact that increased movement of the diaphragm on the dependent side compensated for decreased movement of the ribs and vice versa and, furthermore, that it was very doubtful if lying on one side decreased in any amount the respiratory function of that lung. This has apparently been recently confirmed (Pier-son and Newell). If, on the other hand, the diaphragm be paralyzed, then postural rest may prove to be more efficacious. Following the phrenic operation I have used in some patients a shot bag on the chest and have raised the foot of the bed 12 inches. Some of the patients have improved. The use of weights on the abdomen, especially when the left lung is affected, and compression of the abdomen by belts, so helpful in some cases of emphysema, should be more beneficial after a phrenic operation.

A successful thoracoplasty is a highly satisfactory operation. It lingers ever in the back of the mind of both patient and physician, and in the front of the mind of most thoracic surgeons. The immediate results have been greatly improved in skillful hands. It has saved many patients from a speedy death. The ultimate results at the end of five and 10 years have been confused by the frequent improvements in technic and failure to state the condition of the patient at the time of rib removal. The operation has come to stay and it behooves all of us to become familiar with its indications. It often frees the sputum of bacilli, decreases the amount of sputum if any persists after operation, and enables a hopeless invalid to resume a normal life. I shall await with great interest to see how these patients weather the respiratory storms so common during the colder months.

There are other surgical procedures, bilateral artificial pneumothorax, oleothorax, apicolysis, plombage, intercostal neurectomy, excision of the lung, all of which have had their uses and advocates.

Before passing on I should like to emphasize the fact that none of the surgical measures which I have recommended excise the diseased area. These procedures act mechanically to put the lung more or less at rest and so to limit the poisoning, to relax the lung, and to place it finally in such a posi-

tion that the simple measures mentioned under the discussion of the treatment of the "minimal" may now become effective for the "advanced" patients

Now since the therapeutic quadriad is apparently necessary in all instances, it is desirable to decide where it can best be put into practice. For those below a certain economic level, the sanatorium or sanatorium-hospital, rarely a general hospital, is best. The more newly constructed institutions are built really for affording rest for patients, and in them every bed is a "hospital" bed, and all the measures advocated for hastening the formation of fibrosis can be used. Many of the economically independent, under a well trained physician, also do remarkably well at home, so well indeed that change of climate, formerly so strongly advocated, is now neglected to the loss of a certain number of patients. All climates might be divided into two groups, sedative and stimulating. Why some are stimulating is difficult to say. As recovery with or without operative measures depends upon the formation of new connective tissue, increased stimulation would seem in some cases advisable. This may be had, as Dr. Trudeau long ago said, in the middle of the ocean, in the midst of the sands of the desert, or on the mountain. Many may not, as I have said, require this, some unquestionably do.

Complications of pulmonary tuberculosis are apparently growing less frequent. A satisfactory method for the diagnosis of secondary intestinal tuberculosis has been followed by numerous recoveries, after the use of heliotherapy or high vitamin diet, whereas formerly, death usually sooner or later supervened. Laryngeal tuberculosis, considered a fatal complication 30 to 40 years ago, now yields to vocal rest, electrocauterization and heliotherapy. Diabetics, after the onset of pulmonary tuberculosis, formerly usually died when put on the diet considered necessary for the tuberculosis, but now with insulin, and the diet required for the diabetes, they frequently recover. The pleural complications, not uncommon in artificial pneumothorax, and at first so dangerous, now yield to the attack by physician and surgeon. The treatment of the complication of pregnancy depends upon how the patient stands pregnancy, whether the predominating type of disease is exudative or proliferative, and how she can be cared for during and following pregnancy. In active disease, prevention of conception is to be preferred to abortion, which should not be attempted after the third month. Artificial pneumothorax may help many patients to bear one or more children safely.

Syphilis should be treated somewhat mildly while pursuing the usual treatment for the pulmonary tuberculosis.

The medicinal treatment has at present few advocates for no substance has been found that can destroy the bacilli and their contained poisons and not injure the host. The destruction indeed of the bacilli in large enough quantities would, on account of the allergic state, bring most patients to the brink of the grave or totter them into it. The only hopeful result from

chemotherapy so far has been the gold salts. In certain instances they have been found helpful. Search for a new tuberculin, which still goes on, is a confession of a present lack of the desired results. BCG, practically a preventive vaccine, is not for use in treatment. Heliotherapy and roentgenotherapy in uncomplicated pulmonary tuberculosis have afforded no convincing proof of their aid. Psychotherapy, used consciously or unconsciously, by all practising physicians, is still as important as it was in the days of Hippocrates. Occupational therapy has helped many to pass the dragging hours of rest.

Finally I would like to emphasize the thought that recovery from pulmonary tuberculosis depends not only upon what we do for the patient but much upon what he brings with him to the physician, in his head as well as in his lungs. We can assist, but do we improve upon the *vis medicatrix naturae* as brought about by rest, food, air and education?

TUBERCULOSIS AMONG STUDENT NURSES A FIVE YEAR STUDY AT BELLEVUE HOSPITAL *

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THIS study was undertaken to collect accurate information about the incidence of tuberculosis among student nurses, to test the efficacy of a system of early diagnosis and case finding, and to measure the results of a rather rigid system of rest treatment in the cases found. Previously, like many others, we had observed a great deal of tuberculosis in nurses but could only infer its duration, rate of progression and relation to hospital service. Such inferences do not answer obviously important questions. A planned study is necessary, and this must be continued for a period of years. Because of the insidious and variable behavior of the disease, a five years' study was considered to be the minimum needed for our purposes. Accordingly it was started in February 1931.

Bellevue Hospital is a municipal institution with a normal bed capacity of 2333, in addition to an outpatient department registering 2171 visits daily. All types of cases, excepting the acute contagious diseases of childhood, are accepted. The Tuberculosis Service has 174 beds. Tuberculous patients who require specialized treatment, such as surgery, are accommodated on wards of the service concerned. Overcrowding is almost constant in Bellevue. The Tuberculosis Service, for instance, often has an excess of 40 to 100 patients, who are accommodated in cots in the center of the wards and, at unusual times, also in the corridors. In the last five years from 3100 to 3600 patients have been admitted to the Tuberculosis Service each year, 15 to 20 per cent of these cases are found not to be tuberculous. According to accepted standards, the nursing personnel is usually inadequate numerically, and at times the duties of the nurses are extremely arduous.

The nursing staff is made up approximately as follows: graduates (male and female) 625, students (female) Bellevue School of Nursing, 200, students (male) Mills School of Nursing, 67, affiliating students (male and female) 121, preliminary students (female) 45, total 1058. This study is limited to female students of the Bellevue School of Nursing. On admission to the school these women average from 18 to 20 years of age. About half come from cities and half from the country and small towns. One class enters in February and one in September of each year, the number of students in a class varying from 25 to 65. The duration of the course is three years. Upon being accepted for training the nurses see

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service in practically all hospital departments. The hours of duty, not including classes, are eight daily for six days a week. One month is spent on the tuberculosis service after the beginning of the second year of training. Here, as in all other departments, the nurses wear gowns when ministering to patients, but do not wear face masks. Cleanliness, especially frequent washing of the hands, is urged upon all nurses, but "contagion technic" is not employed.

Selection of Candidates The selection of young women to undertake the arduous course of training is an important task. Up to September 1933, suitable candidates were accepted for the usual probational period, but, since then, a different and more effective plan has been followed. All candidates now spend a preliminary two weeks' "orientation period" before selections are made. During this time the Health Service of the School, under the direction of Miss Mary M. Sullivan, subjects each candidate to a rigid examination including family, social and personal history, a general physical examination, urinalysis, hemoglobin estimation, chest roentgen-ray, Mantoux tuberculin test, and a psychiatric interview. Personality, emotional stability and intelligence are studied. On the bases of the findings during the "orientation period," the women who fail to qualify physically, mentally, emotionally or otherwise are rejected.

Approximately 8 to 10 per cent of the candidates are rejected during these two weeks. The main physical reasons for rejection have been organic heart disease, established hypertension, general asthenia and tuberculosis. Among 591 candidates examined by roentgen-ray during our five years' study, seven were rejected because of the discovery of pulmonary tuberculosis. These were young women in apparently good health. The finding by roentgenogram of small nodules or scars, usually apical and presumably tuberculous, or of old calcified deposits in the pulmonary parenchyma or tracheobronchial lymph nodes was not considered reason for rejection, but parenchymal lesions of greater size were so considered, even though some appeared partly fibrotic.

Preliminary Tuberculin Testing During the first week in the school the students received Mantoux tests starting with 0.1 mg. Old Tuberculin (New York City, Department of Health). Those who failed to react were tested during the second week with a dose of 1 mg. O.T. On this basis 312 or 57.9 per cent of 539 candidates were positive to the tuberculin test on coming to the school during the five years' period. Since September 1933, 62.9 per cent of 305 have been positive. It was found that about one-third of those who failed to react to 0.1 mg., did react to 1 mg. O.T. No doubt still more would have reacted to higher doses but probably not in such proportion. In this connection we may mention that three women with gross shadows of calcified tuberculous lesions in the lungs or tracheobronchial lymph nodes or both failed to react to 1 mg. O.T. No discrimination with regard to the results of the tuberculin testing was exercised in the selection or rejection of candidates.

Follow-Up during Training During the first year of training an additional number (about 20 per cent) of students are eliminated from the school, usually because of scholastic failure, but, with few exceptions, the remainder finish the course successfully. Each nurse has a physical examination annually. Illness, when it occurs, is caused chiefly by acute respiratory infection. In the five years' period there was one death, caused by acute appendicitis and peritonitis. No difference was detected in the general health of the tuberculin-negative and tuberculin-positive nurses.

Subsequent tuberculin testing was performed on those negative to 1 mg O T on admission to the school. In this way the incidence of new infection could be determined approximately, although, as stated, such a negative test is not absolute proof that previous infection had not occurred. Retesting was done every six months until a reaction was noted. In a group of 143 such students followed from six months to three years, and for whom we have accurate information, 37 became positive to tuberculin during their first year of training, 37 during the second year and 10 during the third. Among 70 "negatives" followed for the full three years of the course, all but 10 became positive. Thus it is seen that the majority of presumably uninfected nurses became infected some time during their course. An interesting observation was that most of these newly positive skin reactions were severe ("four plus"). No significant relationship could be discovered between the first positive tuberculin test and the character of the preceding hospital service. The Tuberculosis Service appeared no more related in this respect than other hospital departments. There was no way of ascertaining how many of these students acquired their first infection while moving among the people of New York City outside the hospital.

Tuberculosis Case Finding In addition to the admission roentgenogram, every student nurse had a chest roentgenogram (flat film) at the end of each subsequent six months. Routine hospital technic was employed, and reexamination ordered if the films were unsatisfactory. Comparisons were made with preceding films and, in case of the finding of any definitely or questionably abnormal changes, the student was examined and studied by appropriate means. During the six months' interval, additional examinations were done when symptoms indicated. The only important problems for differential diagnosis were pulmonary lesions in three cases which proved to be bronchopneumonia.

The important features of newly developed tuberculosis discovered during these five years are presented in the accompanying table. In short, there were eight cases including six with pulmonary lesions, one sero-fibrinous pleurisy, and one spondylitis. One case was diagnosed in the first year of training, three in the second and four in the third. None except the nurse with pleurisy had fever at the time of diagnosis, and the only constitutional symptoms were usually slight loss of weight and fatigue in five cases. None was aware of symptoms suggestive of tuberculosis. A few fine râles were heard in a single localized area in three of the pulmonary

TABLE I

TABLE I

Case	Diagnosis	Symptoms			Physical signs	Extent of lesion by x-ray	Mantoux test on entering school	Interval between first positive Mantoux and finding of lesion	Tubercle bacilli in sputum	Treatment	Result T, Still under treatment A, Arrested W, Working
		Fever	Other constitutional	Local							
New and Definite Lesions											
M C	Pulmonary tuberculosis	0	0	0	0	3 cm	0	2-3 months?	0	None	A W
J W	Pulmonary tuberculosis	0	0	0	0	0.5 cm	0	1 month	0	None	A W
B D	Pulmonary tuberculosis	0	Slight	Slight cough	Râles	4 cm (later spread)	+		0	Sanatorium and home, 24 months	T
A D	Pulmonary tuberculosis	0	Slight	0	0	2 cm	0 (Calcified pulmonary lesion)	24 months	0	Hospital and sanatorium, 6 months	A T
I I W	Pulmonary tuberculosis	0	0	0	Râles	2 cm	0	13 months	0	Hospital and home, 12 months	A W
R M	Pulmonary tuberculosis	0	Slight	Slight cough	Râles	2 cm	0	13 months	+	Hospital and sanatorium, 12 months	A
M P	Potts' disease	0	Slight	Back pain	Tenderness	One lumbar vertebra	0	1 month (first symptoms)		Hospital 5 months, spinal fusion	T
G S	Serofibrinous pleurisy	Up to 100°	Moderate	Pain chest, cough	Signs of effusion	Moderate effusion	+			Infirmatory and home, 5 months	A W

TABLE I—Continued

Case	Diagnosis	Symptoms			Physical signs	Extent of lesion by x-ray	Mantoux test on entering school	Interval between first positive Mantoux and finding of lesion	Tubercle bacilli in sputum	Treatment	Result T, Still under treatment A, Arrested W, Working
		Fever	Other constitutional	Local							
Preexisting Lesions											
C B	Pulmonary tuberculosis	0	0	0	0	0.5 cm (slight increase in lesion present on admission, later receded)	+		0	None	A W
R B	Tracheobronchial lymphadenitis	0	Moderate	0	0	Moderate enlargement in region of old partly calcified lesions	+			Home 3 months	A W

cases, the other three presented no abnormal signs. None had sputum of any significant amount, and tubercle bacilli were not demonstrated in specimens obtained. Thoracentesis yielded clear serous fluid in the case of pleurisy. The diagnosis of tuberculous spondylitis was made in one case by the orthopedic surgeons on the basis of low back pain and tenderness lasting for three months and the roentgen-ray demonstration of narrowing of an intervertebral space.

The diagnosis of the six pulmonary lesions was made chiefly by roentgenogram. In none of these was the diagnosis suggested by the findings six months previously. The lesions discovered were all presumably of a fresh exudative type. The largest extended from the apex to the second rib on the right and the smallest appeared as a density about 0.5 cm. in diameter. (The diagnosis in this case is questionable, but we include it as being presumably tuberculous.) In the other four the lesions averaged about 2 cm. in diameter, appearing as soft cottony localized patches in the roentgenogram. No cavities were demonstrated. The classification in all cases was Minimal A.

Two additional cases are tabulated in which temporary extensions of old lesions occurred. In one the lesion was a tiny nodule in the pulmonary parenchyma which increased to about 0.5 cm. in diameter and then, by the end of a year, receded to its original size. In the other, a rather marked enlargement of the tracheobronchial and mediastinal lymph nodes, with the symptoms of weight loss and fatigue, occurred. This woman had a number of partly calcified lymph node lesions in this region and also in the cervical region on admission to the school. The swelling subsided within a year, and she has been well and working for a year.

Treatment and Results In two cases with small pulmonary lesions no treatment was advised, and healing has taken place under observation, in one, the tiny focus can no longer be identified. In three other pulmonary cases, strict bed rest was given for two to three months followed by partial rest at home, in one case, and in a sanatorium, in two. The lesions are arrested and healing. In one case, in which bed rest was advised but omitted, an extension of the lesion occurred, but this patient is reported improving under treatment. The nurse with serofibrinous pleurisy recovered completely after five months of bed rest and convalescence and has been working for 18 months. In one case tubercle bacilli were demonstrated in the sputum during treatment.

In these cases, therefore, the lesions were arrested and healed or healing in six and improving in the seventh. No form of collapse therapy has been needed. The nurse with tuberculous spondylitis has recently (February 1936) had a spinal fusion operation and the prognosis is favorable. There have been no deaths from tuberculosis.

Relationship to Tuberculin Sensitiveness Among these freshly developed cases, the Mantoux test as the nurses entered the school was positive in two and negative in six, but in one of the six a calcified tuberculous

focus about 1 cm in diameter was demonstrated by roentgen-ray. If we supplement this small series of cases with observations we have made among other nurses at Bellevue, we do not find any definite trend. In other words, the occurrence and behavior of tuberculosis in all nurses coming under our observation thus far have not varied significantly in relation to the results of preceding tuberculin tests. It should be noted that no freshly developed lesions in the tracheobronchial or mediastinal lymph nodes were demonstrated in those who became tuberculin-sensitive under observation.

Observation after Graduation This study does not include any methodical case finding among the nurses who have graduated from the school. However, the 135 who have graduated in classes included in the study are almost all employed in the hospital and we have their general health records from six months to two years after graduation. During this time one new case of "minimal" pulmonary tuberculosis has been found among the 135 graduates. Two others have had one attack each of erythema nodosum, both have recovered and neither has shown any evidence of tuberculosis. Since the etiology of erythema nodosum is disputed we do not include these among our definite cases. We have no evidence to lead us to believe that the occurrence of erythema nodosum favors the later development of tuberculosis.

Tuberculosis Case Rate Because of the relatively small size of the group included in our study the morbidity rate from tuberculosis during these five years cannot be expected necessarily to represent a definite trend. Another five years' observation will establish this more accurately. Excluding two cases in which the observed changes certainly indicated temporary inflammatory reactions about previously established lesions, the eight cases in which we detected newly developed lesions represent 1.6 per cent of 492 young women who entered the school as students. However, because of variations in the length of observation, these figures have little meaning. The experience is better expressed as follows:

A total of eight nurses developed new tuberculous lesions during the course of training, representing a case rate of 1.09 per 100 nurses per year.

Seven of these were lesions of the lungs or pleura, or 0.95 per 100 per year.

Five of those with pulmonary or pleural lesions required treatment, or 0.68 per 100 per year.

Enumeration of cases, alone, is misleading, especially when the lesions are small, because it affords a very inadequate idea of the actual seriousness of tuberculosis in any group. In six of these eight cases, the lesions have healed or are healing well with or without treatment. According to sanatorium experience, the expectancy of health and life in these six should be very close to normal. In the remaining two (one pulmonary case and one spondylitis) still under treatment the disease may be said to constitute a serious threat, although the prognosis at present seems to be favorable for eventual recovery. Including the three cases under treatment and basing a

tabulation on the entire group of student nurses included in the study, it is indicated that the loss of time on account of tuberculosis during the five years was 27 days per nurse per year

Other Bellevue Nurses It has been shown that tuberculosis in Bellevue student nurses was discovered mainly by regular roentgenographic examination of the chest before the pulmonary lesions had progressed beyond a "minimal" stage, before excavation had occurred, and before definite symptoms had developed. The great value of such a case finding procedure is proved by contrasting our experience with other groups made up of graduate and affiliating student nurses at Bellevue. These groups did not come within our study, and consequently reported for examination as a rule only when they had definite symptoms. Graduates, of course, were more aware than affiliate students of the insidious character of symptoms of tuberculosis. In six years we have discovered tuberculosis in 26 nurses from these two groups. Five had pleurisy with effusion alone. Among graduates we discovered seven minimal lesions, six moderately advanced, and two far advanced, among affiliates, none minimal, five moderately advanced and one far advanced. In both groups, therefore, the lesions were in a moderately or far advanced stage in 67 per cent of the cases when the nurses first developed symptoms sufficiently impressive to indicate to them the need of an examination. This coincides with the experience in the tuberculosis clinics in New York City and in practice generally.

Costs The cost of finished roentgen-ray films for the Bellevue school enrollment was about \$500 a year. Other costs were absorbed in the general functioning of hospital departments and the Health Service of the school. The results, if measured in terms of early diagnosis and prevention of chronic disabling illness, fully justify the expenditure. Economically, it must be considered that early diagnosis saves many thousands of dollars by shortening the period of treatment and restoring nurses to almost full working capacity. One Bellevue graduate, employed in the operating room, was found to have advanced bilateral pulmonary tuberculosis when symptoms first led her to report for examination. She received treatment for five years at a cost of at least five thousand dollars, and at the end of five years she died.

COMMENT

The experience indicates that student nurses entering Bellevue Hospital with negative tuberculin tests became tuberculin sensitive at a rate somewhat in excess of that which would be anticipated in the general community. This observation alone, however, does not suffice to measure the hazard of clinical tuberculosis in relation to that which prevails for the community at large. It must be considered as Dublin¹ finds, that the tuberculosis death rate among white females in the general population ascends to its peak in the 20 to 24 age group. Likewise, there is customarily a striking accretion of new pulmonary lesions. Fellows² reports an incidence of new

lesions of clinical importance among 4000 female employees, aged 18 to 22, in the home office of the Metropolitan Life Insurance Company in New York City, amounting to 0.25 per hundred per year. This rate, established by observation of the group from January 1932, until June 1935, applies to cases in which treatment was usually indicated. In our group the case rate was approximately 0.68 per hundred nurses per year of new pulmonary or pleural lesions requiring treatment, but the incidence of all new lesions was 1.09. The comparison of rates alone, however, is not valid for the following reasons: (1) Our group is small and later observation may reveal a different trend of morbidity, (2) Our cases were found by roentgenogram which is known to reveal more small lesions than the fluoroscopic method which Fellows and his coworkers employ, (3) Tiny pulmonary lesions may appear and recede to insignificant dimensions within a year, and a semi-annual roentgenogram will occasionally reveal one of these which would be missed by an annual fluoroscopy, (4) Fellows' statistics do not include tuberculosis outside the lungs and pleura, (5) Other factors, such as racial stock and time for adaptation to city life, are not considered.

During 1935 the days lost from work on account of tuberculosis by Metropolitan Life Insurance Company home office employees, aged 17 to 35, was 2.6 per female per year. The similarity of our average of 2.7 per nurse per year during the five years' period is interesting, therefore, even though we draw no conclusion from the comparison.

Age distribution of new cases is not known for New York City, but with a death rate of 85, it may be assumed that at least 170 new cases of tuberculosis per 100,000 females in this age group are reported to the Board of Health annually, that these are almost all symptomatic cases, that they are cases of advanced disease in at least 70 per cent of the instances, and that they represent only a fraction of newly developed lesions. Therefore, while we have no basis of comparison for all newly developed lesions, it is clear that, with the system of case finding and control described, the hazard of serious and advanced tuberculosis for Bellevue student nurses has not exceeded that for young women pursuing other occupations in the City.

During the past six years, 50 young physicians have served as resident physicians or interns, some for six months and most for at least one year, on the Tuberculosis Service. Two, both women, are known to have developed clinical pulmonary tuberculosis. In one case this was an extension from a fibrotic lesion which was present when the physician came to the Service, in the other, fairly large apparently calcified lesions in the lung and tracheobronchial lymph nodes were identified previously.

In considering this problem as it concerns the nursing and medical profession generally, further methodical studies are needed on which to base fair judgment. It is to be anticipated that the incidence of tuberculosis will continue among nurses who have graduated but, thus far, we have not proved it to exceed the expected community rate. In a recent analysis of death rates by occupation, Whitney³ finds that the standardized mortality

rate from tuberculosis of the respiratory system among male physicians and surgeons in 10 selected states was 23.7 per 100,000 in 1930. This compares with a mortality of 175.3 among all gainfully occupied males, 15 to 64 years of age. Next to lawyers, judges and justices, with a rate of 18.3, physicians and surgeons enjoyed the lowest rate among all gainfully occupied males in these states.

Our study demonstrates anew the remarkable tolerance of adult human beings for infection with the tubercle bacillus, even in an environment where the opportunities for infection are great. It is again apparent that infection is only one factor in the combination which makes for clinical tuberculosis, though it is obviously the necessary one. It is, of course, highly desirable to avoid infection if possible, but at present this is not wholly possible either in Bellevue Hospital or elsewhere in New York. Other safeguards against the development of serious, chronic, disabling and fatal tuberculosis should be set up not only in nursing schools but also among other groups, particularly among young people generally. Methodical case finding in such groups will almost always detect the presence of tuberculosis in its earliest clinical phase—the only phase in which the disease can be considered curable in 80 to 90 per cent of the cases.

CONCLUSION

During the past five years tuberculosis among nurses in the Bellevue Hospital School of Nursing has been controlled so that its seriousness as a disabling and fatal disease does not appear to exceed that expected among young women in other occupations in New York City.

We wish to express our thanks to Miss Mary M. Sullivan, Director of the Health Service of the Bellevue Hospital School of Nursing, for her assistance and cooperation. Acknowledgments are also made for the cooperation of Dr. Clarence E. de la Chapelle, physician to the Health Service, and for the interest and suggestions of Dr. Haynes Harold Fellows, Assistant Medical Director of the Metropolitan Life Insurance Company.

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THE DIAGNOSIS OF SILICOSIS, WITH SPECIAL REFERENCE TO ROENTGENOLOGICAL MANIFESTATIONS *

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BECAUSE conditions caused by the inhalation of dust are so frequently involved in litigation it is necessary that they be defined with the greatest clarity. Our terminology developed forty to fifty years ago, before the pathology of such conditions had been worked out. Pneumoconiosis was the term coined to designate disease of the lungs due to inhaled dust, regardless of its nature. Anthracosis, siderosis, chalicosis, silicosis were specific forms of pneumoconiosis due to inhaled coal, iron, stone dust and silica respectively. All were considered of equal significance as it was believed that any dust was merely a foreign body which, when inhaled in excess, would produce scar tissue. Then came the discovery that silica was different, that it acted like a poison and caused a specific and progressive fibrosis. If the inhalation of iron or coal dust caused damage it was because they were mixed with appreciable quantities of silica. Other dusts, with the exception of the silicate, asbestos, were apparently quite harmless. The search for still other dangerous dusts is being continued but thus far none has been discovered.

The original terminology is firmly fixed in the literature and it is still valuable if it is used intelligently, but not all medical men are yet familiar with these more recent discoveries, and non-medical persons are apt to be confused by the implications of the terms. It would seem preferable to use the term, silicosis, for progressive disease of the lungs produced by inhaled silica dust. If, in addition, the lungs happen to contain significant quantities of coal or iron the compound terms, anthraco-silicosis or sidero-silicosis, are descriptive. Inhalation of relatively pure coal or iron produces no change that should be interpreted as a disease process. They cause pigmentation but this is disease only in the same sense as the callouses on the palms of the hands, or the pigmentation of the skin from prolonged exposure to the sun. Such changes are in a strict sense pathological but they do not interfere with function and are therefore not ordinarily classified as diseases.

For the same reason the writer would prefer to abandon the use of the term, pneumoconiosis. Its implications are too broad, it connotes a *disease* process when actually its user may have in mind a benign pigmentation of the lungs with or without slight proliferative changes. It is sometimes a convenience to the pathologist in making an anatomical diagnosis of a condition due to some dust whose action is not yet defined. It is also a convenience to the roentgenologist, but he cannot see the dust in his shadows as the pathologist can in his sections. Far too frequently the film is labeled "pneumoconiosis" because of a history of dust exposure. To the

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non-medical mind the term means disease with as serious consequences as silicosis. If it is to be retained, pneumoconiosis should be defined as a *condition* of the lungs resulting from the inhalation of dust that may or may not be of clinical significance.

This paper will point out the specific nature of the reaction to silica, it will attempt to show that no other dust, with the exception of asbestos, is known to produce significant amounts of fibrous tissue in the lungs. It will also indicate the important relationships between silicosis and tuberculous infection.

Space will not permit a review of the numerous observations leading to the conclusion that silica is unique among inorganic materials in exciting a progressive fibrosis of the tissues. It must suffice to state that the injection of a suspension of minute silica particles produces a localized acute inflammatory response associated with phagocytosis by mononuclear cells. This is followed by necrosis and subsequent repair characterized by the formation of a nodule of swollen, hyalinized connective tissue fibers. The finer the particles the more rapid the response of the tissues. Within limits the reaction is a progressive one but, being nodular in type, progression is manifested by a slow increase in size of the original area of involvement. Injection of the same amount of the same sized particles of non-siliceous substances like carborundum, emery, diamond, coal, iron oxide, etc., causes a transitory inflammation with phagocytosis but the lesion is not nodular, it is followed by no necrosis, only a few connective tissue cells are formed and none of them form hyaline fibers.

Many observers are of the opinion that the silica particles dissolve and thus poison the tissue, but this contention cannot be proved by chemical methods. Indirect evidence would seem to substantiate this view but silica, or quartz, is only very slightly soluble at the hydrogen-ion concentration and temperature of the body. Reaction to injected silica occurs within an hour or two, which is difficult to reconcile with the solubility hypothesis. The writer believes that silica is a tissue poison but that some property other than solubility is responsible for its irritating effects.

Gunea pigs and other animals made to inhale pure silica dust for eight hours a day, over a period of a year or more, develop nodular fibrosis of the lungs that is quite comparable with the lesions found in human beings with silicosis. Their disease begins with phagocytosis of the dust particles in the air spaces, migration of these dust-containing cells into the lymphatic system, and concentration of the foreign bodies in the areolar tissues along the vessels and at focal points in the lymphoid tissues. Proliferation of the local connective tissues follows, producing perilymphatic sheaths of fibrosis and tubercle-like nodules of fibrosis in the lymphoid tissues. Because of their position the expanding nodules tend to compress the adjacent lymphatic vessels. The free flow of lymph from the lung is impeded and subsequently inhaled dust is more apt to remain in the air spaces.

With the drainage system of the organ impaired the phagocytes tend to carry dust particles into the walls of the air spaces. Proliferation of the connective tissues in this location causes both nodular and diffuse fibrosis. The latter is more prone to occur when the dust concentrations are high and the foreign bodies accumulate much faster than they can be removed by physiological mechanisms. The nodular foci of reaction exhibit the same evolution as that described for injected silica. If the dust accumulates slowly, necrosis is slight and may involve only a few cells at a time, if it accumulates rapidly necrosis may dominate the picture. In rabbits, and sometimes in guinea pigs and human beings, necrosis is ultimately replaced by calcification.

Inhaled mineral *particles* other than silica are phagocytosed by the same kind of cells and many of them removed to the lymphatic system. There is a decided tendency for some of the phagocytes to become overloaded so that their motility is impaired and they remain with their ingested material inside the air spaces. Since much of the dust makes its way to the alveoli beneath the pleura, the surface of the lung is pigmented if a colored dust is involved. These mineral particles do not actively stimulate connective tissue, and no appreciable proliferation occurs. After one or two years of exposure to heavy concentrations of such dusts one finds accumulations in the superficial air spaces, in and along the lymphatic trunks that course through the walls of the vessels, in the lymph nodules inside the lung, and in the lymph nodes at their roots. Such deposits stimulate only the very slightest proliferation of connective tissue. From its location such reaction can hardly affect pulmonary function.

Animals breathing the *fibers* of the silicate, asbestos, show a third type of reaction. A considerable number of these fibers are able to pass the barriers of the upper respiratory tract and to slip along over the surface of the ciliated epithelium lining the bronchi. When they reach the sacculated walls of the respiratory bronchioles they are caught in the lateral alveoli and practically none are carried onward into the terminal air spaces. This type of foreign body seems to present a new and difficult problem to the defense mechanisms. Phagocytes and giant cells attempt to ingest the fibers but they are apparently unable to transport them. Most of the cells remain in and along the walls of the terminal bronchioles where they first lodged, only very rarely can fibers be found in the lymphatic system. In the presence of complicating infection a few may be transported to the lymph nodes.

All of the reactions to fibrous asbestos thus far observed have been confined to the region of the terminal bronchioles. The reactive process starts as a collar of cellular fibrosis about these structures and during a three year period of exposure the only appreciable extension has occurred peripherally along the alveolar ducts given off from the ends of the bronchioles. The ultimate alveolar sacs and alveoli are uninvolved and no reaction is detectable in the lymphatic system. The resultant picture is that of small, isolated patches of fibrosis lying in an otherwise normal lung. The characteristic

asbestosis bodies that are found in human beings are reproduced in guinea pigs. Rabbits have not developed them because their upper respiratory mechanisms are apparently adequate to prevent the penetration of fibers. Their lungs showed no fibrosis.

Only these three general types of reaction have thus far been discovered. The silicosis picture may be modified when the dust causing it contains varying quantities of non-siliceous substances like coal and iron. Under such circumstances the adulterant dust particles are not so uniformly segregated in the superficial air spaces and in the vicinity of the lymphatic system. Many of them are carried to the periphery of the silicotic nodules where they, and some of the silica, are responsible for the formation of an irregularly radiating zone of thin fibrous tissue. This disturbs the usual compact nodular arrangement of the typical silicotic lesion. The matter of protection against silica by adulterant dusts is still under investigation and cannot be discussed here. It is possible that other types of reaction, as unusual as that to asbestos, may sometime be discovered, but thus far only the three that have been described are recognized.

The effects of inhaled silica, asbestos and non-siliceous dusts upon tuberculosis have been tested in experimental animals by administering a primary inhalation infection with attenuated tubercle bacilli. In normal guinea pigs such infection causes a self-limited lesion comparable to the primary complex in man. A year or two after infection most of the tubercles have healed and largely disappeared. In silicotic animals such infection, administered at the time when the dust exposure begins, produces a chronic progressive tuberculosis that usually kills after a period of 18 months to two years. If the infection is introduced when the silicosis is fully developed the animal dies in from one to three months. Inhalation of silica instituted after the infection, when most of the tubercles are healing or healed, causes reactivation and spread from any foci that still harbor living bacilli.

In the case of asbestosis, infection, after the disease is established, runs practically the same course as that in normal control animals. Infection simultaneous with the onset of dust inhalation shows no unusual effects for six to eight months. Then it begins to spread locally in about one-half of the animals, in the others there has been no appreciable effect. Where spread occurred the process was fatal in a few instances, but in animals that survived the acute stages healing and fibrosis were the ultimate outcome. With inert dusts the infection runs a normal course if it is administered when the dust exposure is started. If it is given after some months of dusting it subsequently heals and either resolves or leaves more scar tissues than usual.

These experimental observations have been valuable in interpreting the terminal stages of various human pneumoconioses seen at the autopsy table. They, with the occasional case dying of accidental causes after short exposure, and a large amount of roentgenographic material, have made it

possible to build up pictures of the evolution of these conditions in man. In considering this phase of the subject the roentgenogram will be taken as the point of departure. The various shadows seen in different forms of pneumoconiosis will be explained in the light of known pathological reactions.

In silicosis, the first pathognomonic shadow is that of the fine nodule in the parenchyma of the lung field. Such shadows are discrete, sharply circumscribed, never more than 6 mm., and usually not more than 2 or 3 mm. in diameter, and uniformly distributed throughout both lungs. The inhalation of silica produces other changes before parenchymatous nodulation develops but such changes are not specific and they are readily confused with the reaction to non-siliceous dusts. They consist of an accentuation of the linear markings of the lung due to reaction in and about the lymph trunks traversing the walls of the blood vessels. Perfect stereoroentgenograms may reveal the minute silicotic nodules in the intrapulmonary lymphoid tissues that are situated at the bifurcation of blood vessels. There may also be enlargement of the mediastinal shadow due to the reaction to the silica brought to the tracheobronchial lymph nodes. But such changes are not specific, they may be caused by pulmonary infection. The linear exaggeration is equally well produced by the inhalation of non-siliceous dusts. Therefore, even in the presence of a history of several years' exposure to silica dust, one is not justified in diagnosing silicosis unless he sees the characteristic nodular shadows in the lung fields.

In addition to generalized discrete nodulation, simple silicosis may exhibit massive conglomerations in localized areas of the lungs. The shadows of conglomerate lesions are frequently seen in films of persons exposed to mixtures of silica and other substances like coal. It seems probable that such reaction develops in areas where the lung tissues have been injured by previous infections that have subsequently healed. As the result of the injury more dust, and consequently more fibrosis, occurs in the localized area. Individuals with such pictures have no symptoms of active infection, although they are usually quite dyspneic. Serial reexamination over a period of years reveals no change in the character of the pulmonary shadow.

When tuberculosis is superimposed upon silicosis it may manifest itself as simple superimposition or as a new type of disease known as silico-tuberculosis. The *primary complex* of tuberculosis can be detected on a background of generalized nodulation. The silica rarely has any effect upon these foci as they are generally sterile by the time persons begin to work in dust. Very rarely they have been reactivated and spread in a manner similar to that described in the guinea pig. The scars of healed *apical tuberculosis* are recognizable in the silicotic lung. After prolonged exposures to dust such lesions have been seen to break down and give rise to very chronic silico-tuberculosis, a conglomerate type of disease, that spreads slowly from the vicinity of the original focus harboring bacilli. This lesion is productive rather than exudative in character, cavity formation, if it occurs, is

a late manifestation *Aspiration and bronchogenic* spreads to remote portions of the lungs are limited. The sputum is usually negative until late in the disease. Clinical symptoms of intoxication are slight. Silico-tuberculosis is much more commonly found in the base of the lung than simple tuberculosis. Whether the basal lesion of the silicotic is a manifestation of exogenous reinfection or whether it originates from reactivated latent foci has not been determined.

The focus of silico-tuberculosis may be difficult to differentiate from the conglomerate focus of simple silicosis, but the former being due to an active infection is constantly, though slowly, changing and its bearer will be apt to manifest some clinical evidence of it. Repeated examinations by all available methods are essential for a diagnosis.

Miliary tuberculosis occurs as a terminal event but it is particularly difficult to detect in the roentgenogram showing generalized discrete nodulation.

Pneumonia may complicate silicosis but whether it is any more frequent than in normal populations is debatable. Probably the same factors that favor its development in others are operative in the silicotic. If it occurs, failure of resolution and resultant organization are probably more frequent in the presence of complicating silicosis.

The roentgenographic picture of non-injurious dust reactions has already been mentioned. It is essentially characterized by an increased density and prominence of the linear shadows of the blood vessels in the lungs. This is due to the thickening of their walls from reaction around the lymphatic vessels that they include. There may also be a fine reticulation in the periphery of the lung from reaction about the lymphatics that course through the pleura and interlobular septa. Whether accumulations of dust in the subpleural alveoli intercept enough roentgen-rays to cast a shadow is still debated. It seems doubtful. Healing of an infectious process in a lung containing large quantities of any kind of dust is apt to be less perfect than that in a normal organ. If the infection has been widespread it may leave confusing residua that may be wrongly ascribed to the action of the dust. Such faulty interpretation can be avoided by the study of a sufficient number of persons, exposed to the particular dust in question, to establish a proper standard of comparison.

The pathology of asbestosis in the human subject needs further investigation. Present knowledge is based upon the terminal stages seen in a relatively small number of postmortem examinations. In many of these cases death has occurred from pulmonary infection, which further complicates the picture. Roentgenograms of living tuberculous subjects generally seem to depict a less severe type of reaction than that found in the "uncomplicated" case at the autopsy table.

The roentgenogram of moderately advanced asbestosis is usually characterized by a diffuse "ground glass haziness" throughout the lower parts of the lung fields. As the disease evolves, the haze spreads and the upper portions are involved. In advanced stages there is a generalized, fine

speckling throughout the lungs. The shadows simulate very fine nodulation but they are smaller and less clearly defined. In addition there is sometimes evidence of chronic pleurisy and there may be heavy linear shadows radiating from the borders of the heart. The latter are responsible for a condition labeled "the porcupine heart."

It is not yet clear whether asbestosis in the human being develops in the same fashion as the experimental lesions in guinea pigs. The detection of occasional masses of fibrosis about terminal bronchioles suggests that it does, but in all of the seven human cases that the writer has thus far had opportunity to study there have also been other and more complex fibrous reactions. If one may speculate on the probable pathological reaction responsible for the shadows seen in the roentgenogram, one would infer that the diffuse haziness of the lower lung in moderately advanced disease is caused by the superimposed shadows of innumerable collars of reaction about small terminal bronchioles. It is frequently asked why the first manifestations should appear in only one part of the organ. Probably all portions receive an equal share of inhaled particles if one can trust the appearances seen in human and animal autopsies. The writer's confrere, Dr H. L. Sampson, has suggested that in the thicker layer of tissue penetrated by the roentgen-ray at the base of the lung there would be so many more of these fine lesions that they would cast a shadow, whereas in the thinner upper lung there would not be enough of them to intercept sufficient rays to cast a visible shadow. As these peribronchiolar foci of reaction grew larger and more fibrous with advancing disease they would become more dense and cast definite shadows. The shape of such shadows would vary with the angle of incidence of the rays upon the different lesions, some would appear as rounded spots and others would be elongated. This would explain the fine irregular stippling seen in more advanced cases. The pleural thickenings and linear shadows radiating from the borders of the heart find no explanation in the disease thus far produced in guinea pigs. It is of course possible that longer exposure might cause further changes in the lungs but thus far there has been no hint of such change, unless the asbestosis was complicated by infection. The small amount of human material that the writer has studied also suggested that healed infection was responsible for much of the fibrosis observed. However, this conclusion is provisional and may be modified when further observations become possible.

The incidence of tuberculosis complicating asbestosis is variable in different parts of the world. In Great Britain, Merewether¹ reports 35.7 per cent, in cases that have died, against 59.4 per cent for silicosis. Gloyne² found 17.5 per cent. In this country, Lanza, McConnell and Fehnel³ found only one active case of tuberculosis in 67 cases of silicosis examined by roentgen-ray (1.5 per cent), seven cases showed healed tuberculous lesions. In guinea pigs, it will be recalled, asbestos dust seemed to create some tendency for tuberculous infection to spread but the effect was usually

transitory and was not manifested in all animals Healing was attended by excessive fibrosis

SUMMARY

Regardless of the history of exposure to dust, a diagnosis of silicosis should not be made until generalized discrete nodular shadows are visible in the lung fields. Large localized shadows suggest complicating infection but there is a conglomerate type of simple silicosis that occurs in the absence of active infection. It may result from pulmonary damage by previous infection that has healed. It can only be differentiated from active infection by careful clinical study and by repeated roentgenograms to exclude change in the character and size of the lesion. The silicotic lung may exhibit the usual manifestations of tuberculosis, superimposed upon a background of generalized nodulation, more common are the massive foci of consolidation due to silico-tuberculosis. These may be situated in the upper parts of the lung where they result from reactivated apical foci of tuberculosis but frequently they occur in the mid or lower lung. They consist of a very chronic combination of tuberculosis and silicosis progressing simultaneously in the same area. They give rise to much less pronounced symptoms of intoxication than tuberculosis alone. More acute forms of tuberculosis, aspiration disease, and miliary tuberculosis occur but they are not very common.

Non-siliceous dusts are generally responsible for an exaggeration of the linear markings of the lung. As far as known the slight perilymphatic reactions responsible for them do not interfere with pulmonary function and they do not alter the native susceptibility to tuberculosis.

Asbestosis is not so well understood. The roentgenogram shows a diffuse haziness of the lower lung fields and later a very fine uniform stippling. Whether chronic pleurisy, increased linear markings and conglomerate shadows are due to the dust, to secondary changes incident to collapse of lobules, or to complicating infection, has not been definitely settled. The appearance of a tuberculous lesion in the asbestosis lung is apparently not modified. There may be some tendency toward chronicity.

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SILICOSIS FROM THE PUBLIC HEALTH AND ECONOMIC VIEWPOINT¹

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SILICOSIS is essentially a chronic progressive disease, characterized by an extraordinary tendency to tubercle infection. It occurs only as an occupational disease, and the industrial processes associated with exposure to silica dust vary widely and are distributed over many dissimilar industries.

The time factor in silicosis is a lengthy one. This, together with its progressive nature, tends to complicate and confuse our efforts to deal with the silicotic patient either when he is an applicant for compensation benefits or the subject of litigative or legislative procedure. Obviously, the rate of development in a disease caused by the inhalation of dust is determined by several factors. There are the amount of free silica in the dust, the amount of dust in the atmosphere, and the extent of exposure of the individual. We estimate the severity of the hazard in any given case by weighing these three factors.

Where the amount of free silica in the dust is very high—80, 90, or 95 per cent—and the quantity of dust excessively large and the exposure constant, then the physician sees the severe or, as Gardner has termed it, the classical form of silicosis, which develops in from five to ten years, progresses steadily, and almost inevitably is complicated with a tubercle infection which runs its course fairly rapidly. This is the type of silicosis described in the early literature and found especially in mines where the rock was highly siliceous and drilling was done dry and no adequate preventive measures were enforced—a type of silicosis which is disappearing and will soon be relatively infrequent in this country.

Spread throughout industry are many dust hazards in which the combined weight of the three factors is less than under the conditions just described—the amount of silica may be relatively low—15 to 50 per cent—the quantity of the dust may not be so excessive, the exposure may be less constant, and more or less effective efforts at dust control may be attempted. In this situation, the clinical picture is one of very slow development, made evident only in the higher age groups, with little disability in the absence of infection, and a less pronounced incidence of tuberculosis.

In between the very severe and the mild types of silicosis are many gradations, resulting from the emphasis or lack of emphasis of one or more of the factors mentioned. I desire to stress the importance of establishing and evaluating these causative factors in every case of silicosis. The failure to do so has been largely responsible for much of the misapprehension and

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confusion that have characterized attempts to deal with the silicosis problem during the last few years

The extent of the exposure to the silicosis hazard is greater than might be supposed. The following figures are quoted from a study of the subject by Vane and the author¹. We estimated that there are about 115,000 miners in metal mines and coal mines exposed to silica dust—by no means all of the men employed in these industries. Workers in smelters, foundries, glass works, together with those employed as grinders, sandblasters, and vitreous enamellers, would account for about 325,000. Including also various other occupations with a known silica hazard, we arrived at a total of not less than 500,000 workers exposed to silicosis in this country and this, in our opinion, is a very conservative estimate.

At any rate, the burden of silicosis, both in sickness and in cost, is staggering. From the viewpoint of public health and preventive medicine, it is a shining target to shoot at. The situation is not new. What is new is the attention that has been focused on pulmonary dust diseases in the last five years, with the consequent tendency to include silicosis among the compensable diseases. The difficulties of applying the principles of compensation to an insidious and chronic disease are apparent. It is not my purpose to discuss them here. But it would seem that if these vexatious difficulties are to be overcome, a competent medical board should be an integral part of the compensation mechanism. It is, perhaps, too much to hope that there should be uniformity in the practice of the different States with respect to a standardized diagnostic procedure, but unless competent medical assistance can be made available in carrying out the provisions of occupational disease compensation laws, they cannot be administered with justice nor with a proper regard for the public interest.

The control and prevention of silicosis is, in the main, a medical problem. Upon the physician falls the responsibility of accurate and precise diagnosis—first, to determine whether the applicant for work, where a dust hazard may be present, is free from pulmonary or other disease which should bar him from such employment, and second, to discover as early as possible the indications of harmful effects among those employed. As a judge, deciding who should or who should not work in any given occupation, where an occupational disease hazard is involved, the physician renders a service to the public health as important and exacting as any professional function he may be called on to fulfill. I dwell upon this because it seems inevitable that the physician is going to be interjected into the industrial picture to an increasing extent. While it may be desirable to set up standards of employment in this matter of occupational disease hazards, such standards must be very general. There is no substitute for the personal judgment and experience of the physician, coupled with a first hand knowledge of working conditions. Each individual is a case in himself, and social and economic conditions may demand consideration as well as his physical condition.

The mitigation of the dust hazards falls within the realm of the engineer but the proof of the efficiency of engineering control methods must be determined by the presence or absence of specific pathological changes in the individuals involved. In any situation where silica dust may be a hazard, the information we seek is the percentage of silica in the dust and the number of million particles per cubic foot of air in the working place. The method of sampling and analyzing dust air in working places has been standardized by the United States Public Health Service and the United States Bureau of Mines. Their technic has been generally adopted by competent investigators. The air sample is taken with the Greenberg-Smith impinger, large samples averaging about 100 cubic feet being secured on a level with the workman's face and at a rate approximating that of normal breathing. The sample is analyzed for free silica, and from microscopic preparations the particles are counted and the size-frequency determined. Under most industrial conditions, about 90 per cent of the particles are under ten microns in size. While dust determinations do not come within the physician's duties, he should be able to evaluate the information obtained, otherwise he cannot determine who should be employed and who should be rejected, nor who should be transferred to another job, and who retained.

Workmen exposed to a silica hazard should be examined periodically. An annual examination may be sufficient but the judgment of the physician must be the deciding factor and he should have the right to reexamine those under his care as often as he deems advisable. When a workman is found to have silicosis, he should be protected from further dust exposure—if necessary transferred to another job. When a silicotic becomes tuberculous, he should be placed upon complete disability, both in his own interest and that of his fellow workmen.

From the point of view of diagnosis the value of the roentgenogram has been stressed. While it is true that a roentgen-ray film of the chest is essential, it should be recognized that there is a tendency to disregard other necessary and important diagnostic information. It is a common occurrence for films to be sent to our office for confirmation of a diagnosis with no case history or clinical data whatsoever. A complete occupational history as well as a clinical history, and a thorough physical examination are necessary if the film is to be correctly interpreted. It is also vitally important that the physician who attempts the diagnosis of silicosis be familiar with the general appearance of chest films of working men so that he may be conversant with the various appearances that are compatible with what has been aptly termed "the healthy chest."

The attention that has been centered upon the various pneumoconioses in the last few years has revealed the tendency to disregard occupation as one of the important factors in the clinical history of patients who come from the wage earning class. It is unusual to find an accurate occupational history in either private or institutional records, which is one of the reasons why occupational diseases are not diagnosed more frequently. Espe-

cially where the disease is essentially chronic, as in silicosis, a careful building up of the work history of the patient, from the time he left school to earn his living, may be the only key that will unlock a diagnostic puzzle

I would also like to point out that the clinical picture of silicosis among negroes is not the same as among whites. The negro is not as resistant to silica dust, he becomes tuberculous more readily and he succumbs more quickly. Where the silica dust exposure has been very severe, the clinical picture among negroes may approach the acute in type whereas among white men, working on the same job, it will be characteristically chronic.

An important phase of the silicosis problem is the incidence of tuberculous infection among the families of silicotics. In the early literature, especially that relating to the mining industry, the widow who had buried several husbands with miner's consumption was much in evidence. From this arose the general belief that there was not much spread of infection from silicotics with tuberculosis to their families. Undoubtedly, the situation varies locally and is influenced by race, general hygienic conditions and the severity of the hazard.

As a rule, the silicotic does not live long after his tuberculosis becomes open. Cummings of Saranac, in a study made in the Picher, Oklahoma District (unpublished) found evidence of tubercle infection in over 50 per cent of the children under 16 living in contact with silicotic patients having a positive sputum, but the infection was entirely of the primary type and there was no progressive adult tuberculosis. The whole subject of infection needs further study. We do not know what is the nature of the affinity between silica and the tubercle bacillus.

It is, unfortunately, a characteristic of silicosis that it tends to progress even when there is no longer an exposure to silica dust. The workman with a considerable degree of silicosis has an unfavorable prognosis even though he is removed from further dust exposure. He will probably succumb to tuberculosis. Where the damage to the lungs is slight, or moderate, he may go on for many years with little or no disability, but the overall mortality from respiratory diseases, particularly tuberculosis, among the silica dusty trades bears ample witness to the harmfulness that lies inherent in exposure to silica.

One of the difficulties that is constantly present in dealing with individual cases of silicosis is the estimation of the degree of disability. We would expect this in any chronic disease. The roentgen-ray film is not a satisfactory criterion. There may be evidence of a considerable amount of pathologic change in the film and yet the patient may look fairly well and be conscious of little impairment of his working ability. Chest expansion gives us no clue and little can be estimated from the patient's statements concerning dyspnea except in the advanced cases. Furthermore, it is not always possible to be certain of the presence or absence of infection—either from the symptoms or the roentgen-ray film. As a result, there has been a definite tendency to award compensation or other benefits on the basis of

a diagnosis rather than on actual disability—a most unsatisfactory condition of affairs. Some promising research has been started for the purpose of estimating impairment of pulmonary function without as yet producing results that can be converted into procedures for the clinician.

To sum up, silicosis is a widespread disease and is responsible for much tuberculosis among wage-earners. Its detection and control depend upon the accuracy and timeliness of diagnosis. As with other phases of the public health, successful achievement rests with the physician.

REFERENCE

- 1 LANZA, A J, and VANE, R J. The prevalence of silicosis in the general population and its effects upon the incidence of tuberculosis, *Am Rev Tuberc*, 1934, *xxix*, 8-16.

DIABETES TODAY AND TOMORROW *

By ELLIOTT P JOSLIN, M D , F A C P , *Boston, Massachusetts*

The Hagedorn Era Today we are standing on the threshold of a new era in diabetes The Banting Era which we are now leaving was wonderful, and, even more, it was awe-inspiring During these last 14 years you and I have seen diabetics gain hope, food, strength, insulin has breathed life into their dry bones and they stand upon their feet, a mighty army Yet complications, although lessened in number and severity, persist and—I almost blush to admit it—diabetic coma is allowed to prowl about and decimate our diabetics by seizing the innocent, because undiagnosed, the ignorant and the careless Therefore we have good reason to welcome the discovery of protamine insulin The results with it in the hands of others and with my own patients are so distinctive that for me they amply suffice to name the new era in diabetes after its discoverer—the Hagedorn Era

It is not so much that with protamine insulin the blood sugar of the diabetic can be kept normal for the 24 hours, as it is that along with a normal blood sugar we can infer that there will be glycogen in the liver and muscles, a normal content of fat in the blood and freedom from acidosis, in short, a far more nearly normal bodily mechanism is made available for the diabetic But in a broader sense Dr Hagedorn's discovery is noteworthy He has made treatment with insulin safer and simpler and in so doing will multiply its use by practitioners and patients with consequent reduction in the complications and mortality of the disease Protamine insulin cannot help raising the standard of diabetic treatment throughout the world His discovery already is stimulating other discoveries in the technic of manufacture and administration of insulin The old insulin was so good that we were too satisfied with it There was too much of a *noli me tangere* idea about it That conception has now been broken by Dr Hagedorn and there will be a greater freedom in the world for various improvements in insulin medication Finally, and perhaps best of all, he has demonstrated so plainly that all can read its force that what we need most in medicine today is not more beds for our patients, but more brains for their better care

Not such a very great deal is yet known about protamine insulin There are the two articles from the Steno Memorial Hospital in Copenhagen and the George F Baker Clinic in Boston, in the January 18 number of the *Journal of the American Medical Association*, a monograph by Krarup, one of Hagedorn's pupils, and I have been privileged to see another This is to appear eventually in the *Journal of the American Medical Association*, and in it Hansen, another of Hagedorn's assistants, shows that with protamine

* Presented at the Detroit meeting of the American College of Physicians, March 2, 1936

insulin the large livers of diabetics will decrease in size. Consequently I will recount briefly our experience at the George F. Baker Clinic and supplement it with information I have gathered elsewhere.

Professor Charles H. Best of Toronto showed my patients a week ago today various lantern slides illustrating the effects of ordinary insulin and protamine insulin when given to depancreatized dogs. With one dose of ordinary insulin the dog excreted 25 grams of glucose in 24 hours, but with one dose of protamine insulin the amount excreted was 1 gram. In the one instance the blood sugar after eight hours began to rise to high levels, in the other it remained practically normal for the 24 hour period. I will show two slides, already published by our group in the *Journal of the American Medical Association*, which illustrate the comparison between the short and prolonged action of a single dose of insulin and protamine insulin when given to a normal individual and the treatment of a diabetic by the two methods with the abolition of peaks and valleys and the flattening of the blood sugar curves. (These and various other slides were demonstrated.) They illustrate by blood sugar curves (1) the high morning fasting blood sugar which so often characterizes the patient treated with old insulin and the normal rising blood sugar if treated by the protamine insulin, (2) the reduction of the blood sugar using one dose of old in the morning and new insulin at night, (3) the use of protamine insulin entirely, (4) the reduction of four doses of old insulin to two of the new and of two doses to one.

Eighty of our patients have been treated with protamine insulin since July 1935. Insulin for about one-fourth of these has been furnished us by Dr. Hagedorn and the remainder by the Eli Lilly Company. The action of the two has been similar. We have treated young and old, mild and severe cases, some of short, many of long duration, complicated and uncomplicated, including surgical, obstetrical, those with normal and those with high blood pressure and cases with infections. There have been no allergic reactions. Dr. Long this morning told me there had been one marked allergic reaction proved to be due to the protamine in one of his cases. There have been no abscesses despite the patients mixing the protamine with the insulin in their own homes. Reactions have occurred and recently we have observed more than at first because we have taken more liberties with the protamine insulin. I think only once has glucose been given intravenously for a reaction, but we have given up to about 50 grams by mouth. Reactions have appeared more than 14 hours after a dose and several times with children before the morning insulin. Reactions are less apt to occur with a correspondingly low blood sugar with protamine insulin than with regular insulin. Usually the reactions have been mild and with warning, but occasionally they have been quite severe and prolonged. The reason for this has been that we have used more insulin than necessary in an attempt to gain quick control of the glycosuria. To transfer from old to new insulin in a patient taking four doses requires from a week to ten days. At first one is often discouraged. As a rule we have used, as did

Hagedorn, old insulin before breakfast and new insulin before the evening meal, but of late more and more we have turned to new insulin morning and night. Hagedorn used a diet of carbohydrate 110, protein 73, fat 161 grams, with a large proportion of it at breakfast. We have used the more usual American diet of carbohydrate 150 to 175, protein 75, and fat 100 grams, and occasionally more carbohydrate, but it is possible that it would be wiser to keep at 150 grams carbohydrate, particularly as it is probable that with protamine insulin lipemia and large livers can be avoided.

Protamine is easily obtained for the new insulin. At first it was supposed that after the protamine was mixed with the insulin, the mixture would keep for only one or two days. We have found it effective after 14 days and Professor Best told me it remained stable, if placed in an ice chest, for a month, or, in other words, after making the mixture the contents of the bottle would be used up before it deteriorated. Professor Best also told me it was desirable to wait for 24 hours after mixing the insulin and protamine before administration to the patient. The vial should be shaken before withdrawing the mixture, and in cleaning the syringe, if alcohol is used for sterilization, the syringe should be allowed to dry before inserting it into the vial.

I believe many advances can be made in adjustments of diets and dosages of the old and new insulin to the needs of the patients. In our clinic we are concentrating again upon blood sugar tests, five daily, to determine how we can improve our methods and establish rules of procedure. I shall take pains at the meeting of the American Medical Association in Kansas City to arrange that one of the booths in the Diabetic Exhibit shall be devoted to protamine insulin and shall secure for it charts and ideas from several clinics and arrange that many different clinicians describe their experiences with it and the methods they have found most useful.

No patient who has begun the new insulin has asked to be returned to the old variety.*

One mother says, "Dr. Joslin, we had not had a real night's sleep since Ruthie had that bad reaction eight years ago, but now we sleep all night without a thought of Ruthie, and even in another room. She has had protamine insulin five months. You have no idea what it means to us. I would love to have you tell everybody."

And now I will take up certain features characteristic of diabetes of today.

Diabetes Is a Life-Long Disease I like to think of it as having begun with the tiniest baby in his bassinet and ending only with the last breath of life of the old man or woman. To be sure, we do not recognize the future diabetic in the nursery, and it is only in the last few months that I have realized that this also holds for the latter end of life. Indeed, only 63 per cent of my recent patients in Massachusetts when they died were classi-

* July 16, 1936. Correction of proof allows me to report that two of my patients have asked to be returned to the old insulin.

fied as diabetics. It is true 13 per cent had the word diabetes on the certificate, but escaped enumeration because other diseases took preference. Of the remainder who did not have the word diabetes on the certificate, 13 per cent would have been classified as diabetics if it had been placed there, but the remaining 11 per cent would not have been so classified. I object! At least our diabetics should have the recognition of dying *with* the disease, even all the more if they do not die *of* it.

Heredity Diabetes is an out and out hereditary disease. The individual who is to have it is born with it. To a considerable extent it is our fault that we do not appreciate the possibility of a baby developing the disease, and this is, first, because we have not studied sufficiently its family heredity, and second, because as yet you and I have not been bright enough to invent methods which will show the congenital tendency to the disease. We want to be able "to look into the seeds of time and say which grain will grow and which will not," which child will eventually become a diabetic, and which will be guaranteed to be free from the disease. That is a pretty *arbeit* for us all to work out. Someone discovered blood groupings. Why should not somebody discover a method by which the seeds of diabetes can be detected? Himsworth has recently made a praiseworthy attempt to solve it, although his conclusions that it is the result of a relatively low carbohydrate high fat diet I consider erroneous, first because he assumes that one can argue from mortality statistics to incidence statistics and second because he leaves out of account the all important age-of-onset factor and its relation to the age of the population.

I will show the slide which, to me, is the most convincing of the data assembled by Priscilla White as evidence of heredity of diabetes. Upon it you will note the incidence of the disease in the control population and in the diabetic population. But, most of all, I would point out the incidence in dissimilar twins contrasted with the overwhelmingly high incidence of diabetes in similar twins.

TABLE I

The Incidence of Diabetes in the Siblings of (1) Non-Diabetics, (2) Diabetics, (a) Dissimilar Twins and (b) Similar Twins

Type of population	Siblings number	Per cent diabetic
1 Non-diabetics	682	0.6
2 Diabetics	2385	5.0
a Dissimilar twins	16	12.0
b Similar twins	13	70.0

Age of Onset of Diabetes If we can assume that children are born with a tendency to the disease, when is it likely that the disease will become manifest? To this question we now have an answer, an almost uncanny answer, because of the similarity of onset by decades, no matter whether data are assembled in one clinic from time to time or in a group of clinics.

Suppose two diabetics marry and have a hundred children. These hundred children are fore-ordained and predestined to develop their diabetes according to a definite percentage for each decade from youth to extreme old age. Not all of the hundred will live to develop the disease, because many, as a matter of fact slightly more than half—56 per cent—will succumb to other causes, but the data are so definite that we can look ahead and form an idea of what percentage of these children will appear in each 10 years. This is shown in table 2.

TABLE II

Age of Onset of Diabetes—9853 Cases Male 4639 Female 5214

Decade	Per cent appearing in each decade	
	Males	Females
1	4.96	4.45
2	7.24	6.27
3	9.57	6.08
4	13.75	10.84
5	23.32	22.96
6	24.19	30.25
7	13.65	15.76
8	3.23	3.14
9	0.09	0.15
Totals	100.00	100.00

You will notice from the table based on the onset of diabetes that 5 per cent of the number will appear in the first decade, that the increase is slight in the second, incidentally, there is a definite rise at puberty, that the percentage doubles in the third, again doubles in the course of the fourth and fifth, rising in the sixth to a peak of 24 per cent for males and 30 per cent for females and then falls off rapidly in the seventh, and by the eighth is even less frequent than in the first. By the ninth it is so low there is practical immunity.

In any consideration of diabetes today, we must appreciate the ages at which diabetes is liable to break out and therefore concentrate our measures to prevent and diagnose it at such periods. I hope you notice the decade at which there is a change in the tide of susceptibility to diabetes, namely that the onset of the disease begins to fall in the seventh decade. Actually the peak is in the sixth decade and at about 55 years. This is very important for us all to bear in mind. If we did not do so, with the rising mortality from diabetes as years go on, we might be confused, just as the public is perplexed and does not understand that the number of cases of the disease is bound to increase until the average age at death of everybody has risen from its present level of 48.7 years (1930) to 55 years. The onset of diabetes in these later decades is not rising and the reason for the high mortality is that younger diabetics have ceased to die and have swelled the mortality for later years.

Duration of Diabetes Diabetes is a life-long disease, because it begins at birth and lasts until death, even though it may be unrecognized at either end of life. But it is also deserving this terminology, because when it becomes manifest, it lasts so long. For this statement I have good proof. Thus, of my 300 glycosuric doctors, the average duration of the disease among the 96 true diabetics who are dead was 11 years, and already among the 155 true diabetics living has reached more than 10 years, and I am sure that in this group there are many who have no intention of laying down their stethoscopes until they have lived out their full length of life. Indeed, of the fatal diabetics, my average diabetic doctor's age at death, 1929 to 1936, was 68.5 years as compared with non-diabetic doctors, 63 years, whereas among my living diabetic doctors the average age is now only 55 years. Think of what these doctors do after they develop diabetes. Who played a leading part in the discovery of pernicious anemia and received a Nobel prize?

My medal diabetics attest the long duration of the disease. Already there are at least 400 of these who have lived longer with the disease than was their lot according to insurance life expectancy tables. The average duration of 981 of my diabetics, who succumbed in the last five years, was 11 years, and as I contemplate the living patients, and especially the living children of whom there are in our group 188 whose diabetic life is over 10 years and of whom at least 53 have lived over 15 years since the onset of their diabetes in their childhood, I am sure that the average individual who develops the disease in 1936 or thereafter, will round out 20 years. For your encouragement, also, I will add that 10 times as many of my fatal cases in the last few years lived over 20 years as prior to 20 years ago. Finally, before 1914 the average age at death of my cases was 44 years, and now like the doctors, it is 63 years.

At the present moment the changing duration of diabetes is forced upon me in another way. In tracing the condition of patients with onset of diabetes under 40 years of age I find it extremely more expensive and time-consuming than hitherto because these patients live so long. When my cases died with an average duration of 5 years it was a simple matter to learn their whereabouts, but now it is extremely difficult, particularly in the case of the females, because they change their names. I suspect in a few years that it will be almost impossible to trace patients, as I have done hitherto, simply because they live so long.

Dr. Philip B. Matz of the Veterans Administration tells me that of 1243 living cases the average age at time of onset of the disease is 32.9 years and already the average duration is 9.1 years. There should be little difficulty in tracing the veterans, and they may furnish us ultimately with our most reliable diabetic statistics.

For the doctors this life-long duration of the diabetic carries a lesson. Doctors practice only about 30 years. When a doctor sees a diabetic patient, unless the doctor is very young, like most of you, the chances are that

his diabetics will outlive him. Here is a two-fold lesson. First of all, learn all you can from each diabetic so that you yourself can profit from the experiences which he goes through, and in the second place, remember that if you want a diabetic for your medical life, you must keep him alive. But how are you going to do it? The only way that anyone can keep a diabetic under observation over a period of years is to study more than the diabetic studies, to be able always to tell him something which he does not know and has not seen in the newspapers, to learn so much about the disease that you can detect his errors, to combine, either in yourself or those associated with you, every particle of knowledge which a student, a social worker, a dietitian, or a nurse has, so that you can help him, and then either teach him yourself or get these friends of yours to have that pleasure. To hold the patient you must be in touch with students and investigators or else be a student and investigator yourself, because otherwise your mind will not be open to the truth and profit by it. If your diabetic wanders to someone else, it is almost invariably your own fault if he does not come back to you. Diabetes is a life-long disease, and to treat it one must approach it from that point of view. The diabetic expects the advice and care which will protect him his entire life.

I count upon diabetes lasting as long as 20 years on the average, because I know you will learn control of the disease. How will you do it? For a discussion of this question I now ask your attention.

Control of Diabetes First of all, we all would like to go further and prevent it. That is more easily said than done because 25 per cent of the population in the United States, according to Priscilla White, are diabetic carriers. This does not mean that they will develop the disease, but they can transmit it if they marry an individual who is also a carrier. To me that vast number of carriers of diabetes, nearly 30,000,000, in our country, makes it preposterous to attempt to institute any extreme measures of prevention along eugenic lines. We can teach one diabetic not to marry another diabetic. We can talk about one diabetic family not marrying into another diabetic family, and all that is useful. However, we must remember that of our 100 children, born of two diabetic parents, only 56 will live long enough to develop the disease, and that if but one parent has the disease and the other is simply a carrier, the number of actual diabetics falls very rapidly. Indeed, if two diabetic carriers marry, the per cent of their children who actually will come down with the disease is only $\frac{1}{2}$ the expectation of 25—12.5 per cent. Of course, this is not an inconsiderable number, but it is very different from saying that 100 per cent of the children will develop the disease.

Furthermore, suppose that a few should develop the disease in the latter years of life. At that period we know it is quite amenable to control and the disease is not so terrible after all. Of course, I firmly believe that more bright men than fools are diabetic, and that there is enough of a pituitary element in the disease to make the diabetic outstanding in brains, as well as

in stature and precocious development I do not approve of two diabetics marrying and having children, but I will not go so far as to say that a diabetic should not marry a non-diabetic in a non-diabetic family and not have children

Heredity is important from another standpoint If we know there is a diabetic heredity in a family, we can seek to prevent those influences which are well recognized as favoring the onset of diabetes in that family The danger of obesity can be preached to parents and children and when we do that we are standing on sure ground because in the adult, obesity is a forerunner of the disease in an extraordinarily high percentage of the cases A good muscular development can be favored on the ground that, from experience with diabetic patients, we know without exercise the treatment of the disease is difficult I will not say that we should make suggestions about the quality of the diet It is safer to restrict the quantity Hims-worth would have us believe a high fat-low carbohydrate diet would predispose to diabetes Rabinowitch, from newspaper reports, appears to have found no diabetics among Esquimaux

Simpler Diagnostic Methods Easier methods in securing a diagnosis of diabetes should be adopted The most annoying group of glycosurics, as I have often said, is the group in which the diagnosis has not been cleared My group of this type is particularly large because it goes back before the days of routine blood sugar tests Even now it is too large, because so often patients do not want to come back for a glucose tolerance test In desperation a few weeks ago I decided to clear up as many patients as possible during the first visit For this purpose, I have given them 50 grams of glucose I tell them frankly that unless the test of the blood is positive in an hour one cannot draw conclusions from it But it was a satisfaction in one week to settle the diagnoses of four borderline cases in this manner, and I suspect that I shall follow up this principle still more Incidentally, think of the saving of costs to the patient and of work to the laboratory

Costs of Treatment Costs of treatment of diabetes constitute an important factor in the treatment of this disease which lasts for life We must consider these costs very seriously from the patient's point of view and from the doctor's point of view No patient should be deprived of treatment on account of the cost In order to protect the physician, arrangements must be made by which blood sugar tests can be done very reasonably or without cost We doctors in the hospital have a great advantage in this regard I feel that some permanent arrangement must be made by which doctors in private practice will be accorded the same relative ease in obtaining blood sugar tests from indigent patients and low income patients as are afforded doctors who happen to have a position on the staff of a hospital

Responsibility of Diabetics Responsibility for their own careers must be assumed more and more by the diabetic of today There are so many of them that unless they demonstrate that they can be independent, self-sus-

taining and make a success in life, a prejudice will arise against the whole group. I think diabetics are a superior race of individuals and therefore anything which can be done on their part to prove this and to show to all that they are not marching in a bonus parade to Washington is desirable. Each diabetic should hoe his own row.

Furthermore, each diabetic should make it his business in life to help another diabetic with encouragement, advice or financial assistance. Diabetics as a class are neither very rich nor very poor. Their interests are one. Realizing this, "Every man should help his fellow."

Treatment Diet The dietetic treatment of diabetes is so generally agreed upon today that consideration of it can be dismissed in a few words. Few there are who do not give their patients carbohydrate between 100 and 200 grams, protein between 60 and 90 grams, and fat enough in calories to enable the patient to maintain a weight which is normal or, in older patients, a trifle below the normal standard. It is not the details of diet and calories that are important, but rather the details of teaching the patient how to use the diet and calories. There are all sorts of methods, and each doctor finds out for himself what is most applicable to his own patients. Book knowledge will not do alone for these patients, they must be taught by illustration. They often learn most from one another. The class method of instruction is of enormous advantage. When I demonstrated to the class the reduction in the Benedict test which followed the use of four drops of the juice of one grape, I did more good than if I had talked about the dangers of eating grapes for an hour. Incidentally, after I did remove four drops of juice from the grape, the grape looked just as large as it did before, and that also impressed the class. I will pass over the diet, because I am sure it would be too much "coals to Newcastle" to speak of it here.

Exercise Exercise should be utilized even more than it is. I would like to show you certain slides which represent experiments conducted by my colleague, Alexander Marble*. All of these slides portray curves which show the effects of exercise as compared with rest with or without insulin fasting before breakfast. The secret lies in insulin. The normal individual and the mild diabetic have insulin, but the severe diabetic must buy it if he wishes to be benefited by exercise. Last year we gave our children insulin between 45 minutes and an hour before breakfast, and the children played more or less after it and thus brought their blood sugars down to a reasonable level before they started to eat.

Camps Our diabetic camps, the last two years, have taught us a great deal about the management of diabetes in children and suggested much which I am sure we can utilize with adults. We were able to keep a child at camp at approximately one-half to one-third of the cost that child would need if he stayed in the hospital. In these various camps we built laboratories, costing from \$200 to \$700, and we were able there to carry on the

* The paper has been accepted for publication in the *Archives of Internal Medicine*

treatment of the diabetic children more efficiently and more efficaciously than in the hospital. We had them all day in both places, but we could provide recreation, could supervise their diets more accurately, and give them more pleasure in the camps.

A Diabetic Boarding School The lesson we learned from the summer camps was that with our diminishing resources we must provide for the care of the diabetic children at other times of the year in similar fashion. This has led to the establishment of what I think is a new idea in the management of children, namely, a Diabetic Boarding School. For practical purposes this is what the Prendergast Preventorium amounts to so far as our diabetics are concerned. Originally at this Preventorium underprivileged children and undernourished children, but no children with tuberculosis, were taken. It is under the control of the Tuberculosis Society. Last year they agreed to take our children at \$10 a week, and we now have 10 children there, and they are supervised by a nurse skilled in their care and under the general direction of Dr. Priscilla White. These children are furnished their education by the City of Boston. Their board is paid either by them individually, or by the Welfare Societies—public or private. We are trying to centralize there, not only all the children—there are not so many of them—who need help away from home, but also other children who cannot be well-cared for at home. During the summer we had between 30 and 40 boys at this camp, but in the winter we have both boys and girls. When one of the children became ill he instantly was moved to the Deaconess Hospital. Camps and boarding schools for the uncomplicated cases—hospitals for emergencies. And now I want an inexpensive boarding house home—convalescent home—convalescent hospital for my older patients!

Wandering Diabetic Nurse for Adults Another idea has developed as a result of our work with children. Originally we employed the Wandering Diabetic Nurse only with our children and indeed Miss Winterbottom still acts as a Wandering Diabetic Nurse for them, but we have found lately that the children are doing so well that they require less of her time. You can hardly guess the type of patient she is helping this winter in their homes. Instead of our youngest patients, she is instructing, teaching and caring for our oldest—the old children above the age of 60 and 70 and even 80 years. Such patients one hesitates to move away from their home environment into a hospital. We have found that her services to these old people are most valuable and of course the cost to the patient is greatly reduced. I commend to you both the idea of a Diabetic Boarding School and the use of a Wandering Diabetic Nurse.

What Is a Wandering Diabetic Nurse? She is a composite of a nurse, a dietitian and a social worker. Few institutions and still fewer outpatient departments and almost no doctors can enlist three separate individuals to care for their diabetics, but each diabetic needs the services represented by these three professions, and the services must not be rendered routinely, but they must be specialized. The individual who assumes the

task of helping in diet, in nursing and in the social adjustments of these patients must be trained and indeed a specialist in diabetic work. Therefore, it is essential to combine all in one and therefore I attach great importance in any undertaking for improvement in the treatment of diabetes to the position of Wandering Diabetic Nurse.

Let me illustrate a little more in detail the desirability and, indeed, necessity, for such an individual. At the New England Deaconess Hospital we have 1200 diabetic admissions a year, but there are few hospitals that have 100 and there are a great many hospitals in smaller communities that do not have 25. When one divides up the total number of patients throughout the year, there is not work enough for three separate individuals and no nurse, dietitian or social worker will acquire experience enough individually to care for these patients properly. If we can center our instruction in one individual, gradually the hospital can develop specialized treatment so that not only its own patients will receive instruction along these different lines, but the instruction will be so good that doctors in the community will wish to take advantage of the service as well. I believe the endowment of a Wandering Diabetic Nurse in a hospital with 100 beds would be of immense advantage to the community, because her services could be drawn upon by physicians within the hospital's area in addition to the work she did actually in the hospital. There she could serve, not only in connection with the care of the diabetic patients in the institution, but also, because of her wide experience, could aid in teaching nurses the treatment of diabetes.

Diabetic Coma You and I know that it is very easy, even in a large hospital with hundreds of diabetics, to overlook cases of diabetic coma. We doctors overlook them. Nurses constantly overlook them and I regret to say that within the last 12 months we had one patient enter and die within 190 minutes of admission with diabetic coma. I am quite sure that such errors exist in other hospitals, and, in fact, I know and have personal cognizance of such errors. In our own case, experienced individuals were so absolutely positive that the patient had hypoglycemia that blood tests were delayed. I will say, however, that I really do not believe that the patient who died would have recovered, even if he had been treated for diabetic coma from the first minute he entered the institution. But my conscience would feel easier if he had been given every possible chance despite a blood sugar over 1000 milligrams, a CO_2 combining power of 2 volumes per cent and a blood pressure doubtfully obtained at 70.

Hospital Instruction Training in a hospital is desirable for practically all diabetics, and especially for those with small means. Gradually we have reduced the length of stay in the hospital from 30 days, prior to the discovery of insulin, to about 7 days, and I judge even less if we exclude cases with gangrene or infections of the feet. A year or two ago I advocated weekend hospital treatments for diabetics and still approve of it. Repeatedly we have patients come in on a Friday or Saturday and go to work

of a Monday. Sometimes they enter for more than one weekend. With lessening available funds to help needy patients, we are shortening more and more our hospital stays. Of course one cannot complete the treatment of a case or expect to do much more than to inaugurate treatment, but this alone is of great advantage and the balance of the treatment can be supervised through a Wandering Diabetic Nurse or by office visits. To secure success from a short hospital stay, the instruction must be concentrated. One cannot give long talks to patients. Recently we again changed our methods and we doctors, individually, give one talk of 30 to 45 minutes each day. This is supplemented by short classes or desk instruction or bed-side instruction by the teaching diabetic nurse in the hospital. More and more, however, I think we are emphasizing the help which one patient can give another. Indeed, over and over again I hear from patients that they will follow treatment, because of the complications which they saw other patients had in hospitals as a result of neglect of treatment. One can tell a patient to follow treatment and keep his feet clean, but the effect produced is nothing compared with seeing a patient who has his leg cut off, because he has neglected his diabetes and carelessly cut a corn. Therefore, just as we have made our money go farther with children by sending them to camps or to a diabetic boarding school and bringing into the hospital only the emergency cases, so now we are more and more bringing into the hospital diabetic cases for short periods and thus are making it possible to double and treble the number of patients who will have an opportunity to learn how to care for their diabetes.

Decision in Surgical Advice. Diabetics, and doctors as well, are dilatory in their decisions. Against our better judgment we are influenced by protests of the patients and delay operations which are indicated. Last year all of us, surgeons and doctors, consented to postpone an operation on an old man because of the faintest possible chance that his foot might heal. It cost the hospital and family at least \$600 and in the end, after months of considerable suffering, the operation was performed. For that same amount of money, 60 children could have had instruction and care of their diabetes and happiness for a week at a diabetic camp. When all the doctors and surgeons are unanimous in their opinion as to what is best to be done for the patient, the procedure should be carried out or the patient should be discharged to the treatment of another institution or doctor in whom he has more confidence.

Close Supervision of Diabetics. Diabetics require closer supervision. In an earlier portion of this paper I called attention to the fact that 10 times as many diabetics live 20 years, or more, now than they did prior to 1915. I did not add, however, that only one diabetic in eight of my last 900 to die, just prior to March 1935, reached this duration. It is perfectly possible, in my opinion, for diabetics on the average to live 20 or more years, but they will not do so by luck. If we want our diabetics to live, we must protect them from needless death, and these deaths today are primarily from

two causes, just as they have been for years past First, deaths from coma and second, deaths from infection, chiefly of the lower extremities There are other needless deaths which make so desirable a renewed effort to avoid them Tuberculosis relatively is far greater among diabetics than in the general population Thus Dr Howard F Root has shown that in Massachusetts it is more than 10 times as common in diabetic children as in the ordinary school child of similar age and two or three times as common in diabetics of all ages

Cancer is steadily increasing and it is of great interest in this connection that cancer of the pancreas is four to five times as frequently observed among diabetics as among non-diabetics This is a problem for continued study My opinion upon cancer may be biased because of proximity to the Palmer branch of the New England Deaconess Hospital in which so many cancer cases are treated

All are aware that coronary thrombosis and angina pectoris are conditions far more frequently observed in diabetics than in non-diabetics, but these are not so easily remedied by observation of the patient They are subjects for research On the other hand, coma, gangrene, osteomyelitis, tuberculosis and cancer are the complications which can be detected early and treated well What is the significance of all this, therefore, in our consideration of diabetes today? In my opinion, we must change our method of treatment Hitherto I have not asked patients to come back regularly for observation, but beginning January 1, 1936, I am telling each patient, specifically young and old, recent case and old case, that he should keep under the supervision of some doctor and be looked over as a routine at least every three months more or less, according to the case I intend to give each patient, in the letter I send him after his visit or on a card, a statement that he should see some doctor at least within three months after his visit to me Most doctors do not like to ask patients to come back for fear they will be accused of grasping for money I know that many of us who see patients for other doctors hesitate to ask patients to come back or even to communicate with them, but I believe it is possible that a more aggressive attitude can be adopted and in doing so the family doctor as well as the patient can be protected At least, I am willing to try an out and out experiment and risk the opprobrium which it may arouse

Coma still causes more deaths in diabetes than it should It is true that the mortality has fallen from 64 per cent (among 325 of my deaths) prior to May 31, 1914, to 6 per cent (among my 981 deaths) ending in March 1935 These figures apply to deaths both in and outside the hospital By and large, however, throughout the country, I suspect that the mortality from coma is still between 10 and 20 per cent How can this be remedied? In general by education of the patient and insistence upon his keeping in touch with his physician and always reporting immediately when any unusual symptoms occur The opportunity for improvement does not rest alone with the patient and with the general practitioner I

know from our own bitter experience that treatment in the hospital can improve. Cases of coma are still unrecognized or confused with other states. My colleague, Dr Root, points out that errors in diagnosis are always to be expected in moribund patients, but he too feels, as I do, that this is no excuse for the delays which sometimes arise, and I fear far more frequently than is generally believed, before the diagnosis of diabetic coma is made after the patient reaches the hospital.

A Coma Drill A coma drill in a hospital is essential, just as is a fire drill. Neglect to have one I think will surely result in unnecessary damage to the patient and the reputation of the hospital. It is easy enough to send a specimen of the blood to the technicians in the laboratory by day, but at midnight and in the early morning hours, when technicians are not available and house officers are out of practice in determination of blood sugars, CO_2 values and non-protein nitrogens, it is very easy indeed for mistakes in analysis to arise. I suggest for your consideration the establishment of a diabetic coma drill in your hospital with records to be kept as to how long it takes to secure blood and make a diagnosis. Minutes count in the treatment of diabetic coma or hypoglycemia and arrangements should be perfected, just as I am sure you already have arrangements perfected for the reception of a coma case into the wards.

Follow-Up of Discharged Cases The sequel of the old man or woman whose toe or leg has been removed, because of diabetic infection or gangrene, has not been encouraging. I hesitate to state the few years which such patients live. My colleague, Dr Root, has been much interested in this, particularly because of his association with Dr McKittrick in compiling the monograph on "Diabetic Surgery." Recently Dr Root has arranged that once a week the relatives of the patients with lesions of the legs should see him for a talk so that they could be prepared for the care of their parents, brother or sister, wife or husband, when discharged. This has proved to be quite worth while. The conference has taken place in the early evening when relatives visit the patients.

Dr Root has also instituted another forward step in that the Wandering Diabetic Nurse sees the patients with a lesion of the lower extremities within 10 days after discharge. The follow-up of this special group of cases has also proved well worth while. As a rule, patients coming with lesions of the lower extremities are patients who are poor. They need supervision at home. We need more organization in their care.

Insulin Insulin gave us a new diabetic to treat. Even now we hardly have begun to realize its benefits. I am sure they are far more than those represented by prolongation of life or reduction of complications. The spirit, as well as the body of the diabetic, has been protected. Today treatment with insulin is so well understood that it is almost automatic and if a doctor is really interested and will read his medical journals or even the standard textbooks, he will not go far astray. No longer do we try to give one large dose (I am speaking of regular insulin, not protamine insulin)

and expose the patients to reactions when two doses will be more efficacious. If three doses are needed, often the third can be taken conveniently on retiring so that an approach to a normal blood sugar can be secured on waking. We all know that insulin works and that if unusual dosage is necessary there is a reason for it and that it is for us to find the reason. Generally the reason lies in an infection, open or concealed. Often it is associated with other glandular trouble. Seldom it is the result of faulty administration, but quite commonly a sequence of a poorly-balanced diet and a previously neglected diabetes. Mrs. St. C. had a severe reaction when the site of her injection was changed. She is an insulin resistant case, taking 400 to 500 units. It is a wonderful step forward that now we realize that insulin will act favorably upon the standard case of diabetes.

None of us are unmindful of errors with insulin, in measuring dosage, in methods of administration, reduced efficiency because of insulin lumps and of the atrophies occasionally developing without known cause. Most of all, however, the dangers of hypoglycemia have been foremost in our thoughts. These have been greater of late than formerly because today with insulin the diabetic is so well that he wanders farther afield and so is under less close supervision.

The Rôle of the Liver and the Interrelation of the Ductless Glands in Diabetes. The liver and the ductless glands are bee hives of experimental activity in diabetes today. That the excessive deposition of fat in the liver can be prevented by choline is a triumph attained by Best and his co-workers in Toronto. The next speaker, Dr. C. N. H. Long, will tell you of the diabetic wonders achieved by the experiments of Houssay upon the pituitary and the new operations involving not only the pituitary, but also the medulla and cortex of the adrenal, which he, in association with his colleague, Francis Lukens, has devised, executed and interpreted. Indeed, Dr. Long's paper will give you a far better idea than mine of what to expect in the Diabetes of Tomorrow.

CLINICAL ASPECTS OF CIRCULATORY DYNAMICS IN ARTERIAL HYPERTENSION *

By ARTHUR R ELLIOTT, M D , L L D , F A C P , *Chicago, Illinois*

WE know that of patients who have persistent high blood pressure a considerable percentage—estimated by some authorities to be as high as 25 per cent—will die of causes that have no bearing whatsoever on their hypertension. The remainder will succumb through development of some condition directly attributable to the prolonged circulatory strain. A small percentage will die of progressive renal insufficiency, resulting from arteriolar changes in the kidney or more likely from progression of an unrecognized obscure nephritis. A larger number will develop cerebral accidents, the so-called hypertensive encephalopathies. The remainder, predominantly the largest group of hypertension casualties, die of cardiac failure. It is with this latter aspect of the ultimate consequences of arterial hypertension that the present discussion is concerned.

Certain facts or inferences emerge from practical experience with the run of cases of high blood pressure. For example it would appear that patients who have a marked hereditary bias toward vascular pathology usually sustain the strain of elevated pressure for longer periods than those without such a background. This is difficult to explain unless it be that certain constitutional resistances enter into their tissue make-up as provision against this inherited liability, and so insure their survival, or perhaps it may be because these individuals develop high pressure earlier in life and more gradually than do others. Another observation common to all experience is that high blood pressure developed in association with or in consequence of certain other disorders may be viewed more tolerantly than when it emerges as a single symptom. For example when it exists in common with diabetes, hyperthyroidism, chronic anemia, uterine fibroids, prostatism, etc., it rarely is as malignant in its effects, and moreover tends to share in the beneficial influence of therapeutic control of its associate. In passing it should be noted that exactly the opposite is true when hypertension results from nephritis. Another well-tolerated form of hypertension is the elevated systolic pressure resulting as a compensatory response in aortic atherosclerosis. This is compatible with long life and reasonable efficiency. I get the impression from a review of my experience that what has been called the neurogenic variety of hypertension has a milder prognosis although usually a more stormy symptomatic course than is true of other forms. The blood pressure in such instances is particularly unstable, being subject to wide fluctuations, so that there is more easement to the cardiac and vascular strain than is available in other cases. These are the

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patients who derive the greatest benefit from appropriate personal hygiene and especially from bed-rest and hospitalization. Other things being equal it is a fact that marked decline in average pressures induced by rest either alone or combined with simple sedative medication foretells a better prognosis. To complete these brief notes on prognosis in arterial hypertension I should revert to the well known fact that the outlook is in all ways more favorable among women than men. They live longer and a higher percentage of them die of causes not connected with their hypertension. This strange fact is not because women do not have pressures as high as those of men. Its significance may lie in some resistance-provision in the female circulatory structures inherent in their biology as a survival factor or in the less strenuous life of the average woman as compared with the average man. Moreover another factor may enter in and that is the influence of the menopause which slows down many women and may thereby prove a buffer mechanism.

This brief reference to certain considerations having bearing on the prognostics of hypertension yields the impression that incidental factors and influences that tend to moderate the persistency and severity of the strain prolong the ability of the heart and vessels to carry the load and that the heart is preponderantly the determinant of the prognosis. The mechanico-pathology of the heart and how it comes about is therefore the great concern and interest in the clinical study of blood pressure.

I need not labor the point that patients coming under observation for the first time with very high pressures and evidences of strain in the cardiovascular apparatus may survive for years even in the face of conditions that appear absolutely to preclude such a prospect. This fact stands as a tribute to the extraordinary capacity of the heart to tolerate profound maladjustments in the dynamics of the circulation. About the only thing, generally speaking, that appears to interfere with this compromise is the presence of coronary artery disease, especially coronary occlusion with infarction of the myocardium, but in exceptional cases even this development may not prove an intolerable handicap.

The work of the heart depends not only on the peripheral resistance but also upon the amount of blood its chambers discharge. Cardiac output has been the subject of study by several investigators but for various reasons no uniformity of opinion as to the reliability of the results secured has been reached. For what they are worth the significance of data accumulated in arterial hypertension appears to prove that basal cardiac output remains unaltered so long as congestive heart failure has not supervened. The findings, imperfect as they may be, yield the general impression that the high pressures of chronic hypertension are neither established nor maintained by an increase in the volume of blood discharged by the ventricle. These findings rather support the conclusion that the exaggerated pressures and consequent increase in heart work are due to increased peripheral resistance re-

sulting from precapillary constriction which is the characteristic feature of hypertension

Inasmuch as the work done by the heart pump is almost entirely spent in overcoming resistance, the fall of pressure from aorta to periphery being extreme, it follows inevitably that the capacity of the ventricle to maintain efficiency in the face of permanent and steadily increasing resistance must in time become exhausted. That this event is so long postponed may be because coronary blood flow is chiefly dependent on aortic pressure, any increase of which results in free flushing of the myocardium. This is a matter of pressure rather than of cardiac output or heart rate which influence the coronary circulation far less. An added beneficial effect on myocardial nutrition may result from the fuller clearance of the vascular stream bed resulting from the slow heart rate and prolonged diastole present during much of the clinical course. As an offset to this advantage stands the undoubted fact that the coronary arteries are in some manner detrimentally affected by continuous increase in blood pressures so that coronary obstruction develops more frequently in these subjects than in any others.

The ultimate effect upon the coronary vessels even without the dramatic event of occlusion is to produce in the majority of cases varying degrees of narrowing of their caliber from sclerosis, often with secondary fibrotic alterations in the muscle fibers throughout a considerable area of the heart wall. That these scarrings are not more frequently detected is perhaps because the gross-pathologist is apt to confine his inspection of the myocardium to a search for infarctions and overlooks less obvious defects. This point has been emphasized by some pathologists, notably by Klotz. The matter is important because we are gradually swinging around to the position that it is not work exhaustion per se that causes the hypertensive heart to fail but interference with the chemical exchanges in the myocardium through progressive restriction of the coronary blood supply. Lowering of the systemic blood pressure cannot necessarily be taken as evidence for or against the existence of widespread coronary disease. There exists no constant ratio as between height of blood pressure and myocardial dysfunction. It is not exceptional to see blood pressure maintained at or near its usual level after coronary occlusion, and many patients retain heightened pressures despite extreme degrees of myocardial failure even up to death itself. It was emphasized years ago by Norris that the last ounce of reserve power of the heart may be put forth in maintaining blood pressure levels and the heart muscle be actually at the point of final failure notwithstanding a pressure well above normal. It is a mistake then to expect necessarily a fall in blood pressure with cardiac failure no matter how induced. This may be because pressures are much more easily influenced by changes in the caliber of the peripheral arterioles than by alterations in cardiac output, and peripheral constriction may be at such a high point that even a small output may suffice to maintain pressures at an abnormal level.

In our zeal to interpret the importance of the heart and the larger vessels of the distributing system it should not be forgotten that these more obvious phenomena are but means to the end that an adequate capillary flow be constantly maintained. This is a point much neglected and yet the picture is not complete if we do not take into account what goes on in the vascular channel distal to the heart and aorta. It is well to remind ourselves that the dynamics of the circulation are not entirely a function of the heart pump. The initial propulsion of the blood appears to be its sole and only function, in short, as Harrington Sainsbury puts it, the heart is a "power chamber." After the cardiac systole is completed diffusion of the blood throughout the circulatory tree becomes the business of the arteries. Inasmuch as systole is shorter in time than diastole it might appear that the arteries absorb a larger share of the work of circulatory movement than does the heart. If there be truth in this assumption then what goes on in the arteries in hypertension becomes of great importance to the fate of these patients. First of all it is well known that the aorta is essentially an elastic tube cunningly devised to receive the oncoming blood from the heart with, as it were, "open arms." After distention follows recoil, allowing the "run off" into the smaller vessels to continue during diastole. These lesser vessels possess little elasticity and though heavily endowed with muscular equipment they have little propulsive power. They are but smooth channels allowing flow without friction or loss of head until the precapillary bed is reached where the stream slows down and pressure sharply declines. There is comparatively small reservoir capacity in the arteries. Such as there is depends on their elastic stretch and this, except in the aorta, is not considerable. Their maximum extensibility lies slightly above the usual systolic pressure in health. Above that limit the cubic enlargement of the arteries is less and less as pressure rises and the heart responds to its increasing labors. It is a mistake to assume that the compensatory hypermyotrophy that thickens and strengthens the heart wall does not affect the arteries in like manner. This is shown in cross sections of these vessels and to the palpating finger they seem rigid and taut. This compensatory reinforcement by the arteries offers a valuable element of collaboration to the heart in carrying on its task in the face of increasing resistance. How important this ancillary action may be is revealed in due time. The unfortunate predicament of the arteries in this circumstance is to be caught between the upper and nether millstones—the strongly acting hypertrophied heart on the one hand and the constricted precapillary bed on the other. During the sthenic or fully compensated stage of hypertension the arteries are observed to be taut or rigid but they are not tortuous. Under the excitant effect of persistent internal overpressure molecular degenerative changes in the vessel walls result and progress until what Norris has designated a "break in vascular compensation" supervenes. This is revealed by a rather rapidly developed tortuosity and relaxation of accessible arteries. We may palpate it best in the brachial and femoral arteries and see it strikingly in the retinal field. The

effect of this relaxation of general arterial tone upon the heart proves unfortunate because thereby is shifted upon that already overworked organ an added burden. For years I have watchfully observed this sequence of arterial events and find reason to regard it as extremely significant. The advent of arterial dilatation often proves to be a forerunner to the development of weakness and failure of the ventricle with the phenomenon of congestive heart failure.

Another arterial phenomenon that will profitably repay study in hypertension is the pulse rate. During the greater part of the clinical course the pulse rate is not increased, indeed it is often slower than normal. In experimental work it has been found that when the heart rate is slowed not only is the blood given a longer time in which to pass the peripheral narrows but the longer diastole allows a more complete filling of the ventricle during its relaxation, thus offsetting the effect of slow rate on cardiac output. Another consideration that may render the slow heart rate of decided benefit is the theoretical deduction based on the known laws of oxygen diffusion that the enlarged heart with its thickened muscle should require a longer time between beats to recover than does the normal sized organ. Since there is no acceleration of rate in most instances of hypertension and little evidence exists of increased stroke volume, an increased minute flow might be assumed. Many workers employing various methods have studied this phase and failed to demonstrate any increase in minute volume flow—indeed it may even be below normal limits. Leaving aside physiologic explanations, which as yet appear to be in a confused state, the clinical fact stands out clearly that a slow pulse rate in hypertension is the best assurance we have of adequate reserve on the part of the heart pump. With increase in heart rate, which in time becomes inevitable, abbreviation of diastole diminishes the inflow quantity of blood thus reducing the amount of blood ejected during systole. Not only does the general circulation decline in proportion to this handicap but, still more important to the patient, the coronary circulation is detrimentally affected by decline in aortic outflow. The thickened muscle fiber of the heart is a decided asset in overcoming arterial resistance but at the same time it suffers from a chemical disadvantage—any decline in coronary flow laying it open to the accumulation of oxygen lack which the myocardium is much less tolerant of than is skeletal muscle. In this manner there comes about with the advent of rapid heart rate a vicious circle tending eventually to produce congestive failure with its train of disadvantages.

Some controversy has existed as to whether the systolic or the diastolic pressure constitutes the breaking strain upon the ventricle. Determination of the time course of the pressure curve in the ventricle shows that no blood is expelled until the maximum tension is developed. During the expulsion of blood into the aorta the pressure in the ventricle remains nearly constant, the curve showing a flat top. This would go to show that the greater part of the work done by the heart muscle is expended in raising the pressure of the blood to the diastolic level and would give that factor the greater im-

portance This seems to be in keeping with clinical experience, for we know that a continuously high diastolic pressure is not well tolerated although per contra a very high systolic pressure may be carried for years without evidence of cardiac exhaustion provided the diastolic pressure remain low This gives the pulse pressure significance merely as a rough index of the mass movement of the blood without any fixed prognostic importance During the stage of adequate compensation the circulation to all appearances is carried on normally In the main the elevated systolic pressure may be considered as evidence of relatively normal heart power and normal blood flow Yet we must not assume that volume flow runs proportional to blood pressure, for the factor of peripheral resistance must be taken into account Neither is it, as already pointed out, correct to infer that an abnormally high blood pressure constitutes an indication of adequate cardiac power Even with the signs of congestive failure present throughout the body blood pressure may still remain considerably above normal Indeed it may be said that there are no definite rules whereby we are altogether safe in judging the import of either a rise or fall of blood pressure In patients seriously embarrassed a rise of pressure may denote restoration of compensation and general improvement, whereas with certain others it may prove unfavorable, implying the advent of uremia On the other hand a fall in pressure levels may prove a favorable indication, signifying lessened toxemia and diminished peripheral constriction Heightened pressure is consequently not necessarily an index of good cardiac response nor is a lowering pressure portentous of approaching cardiac exhaustion The claim that arterial hypertension is a conservative mechanism rendered necessary to maintain an effective working of the organs, especially of the kidneys, does not receive striking confirmation from clinical observation, for many patients appear to profit greatly and suffer no decline in renal elimination when a high blood pressure is lowered by effective treatment To place implicit trust in instrumental readings as an index of progress or for prognosis in any given case is to invite error The patient's general condition and evidence of well-being, his range of efficiency, the presence or absence of well attested signs of circulatory embarrassment constitute better grounds on which to form a judgment than information procurable from blood pressure figures alone with theoretical deductions therefrom

DEXTROCARDIA IN CHILDREN ~

By HENRY A. REISMAN, M.D., F.A.C.P., *Jamaica, N. Y.*

THE term dextrocardia should be employed to designate all instances in which the heart is found in the right side of the thorax. If thus employed, the term loses its connotation as a mere anatomical curiosity, and the study of the etiological types of dextrocardia assumes its rightful importance.

The present discussion of dextrocardia in children is illustrated by reports of eight cases. During the course of a study of tuberculosis in school children, in which the author has participated, roentgenograms of the chests of 11,253 children have been made. In this series three cases of dextrocardia have been found, each illustrating a different etiological factor. Another case in which dextrocardia was caused by a marked scoliosis has not been included in this report. Five more cases which have been encountered by the author among children are briefly summarized.

CASE REPORTS

Case 1 A. Z., male, aged 8 (of the tuberculosis research group), referred for physical examination because dextrocardia was found in the roentgenogram. There were no complaints. He is the only child, and the family history is negative. Birth was normal with no cyanosis. He sat alone and had his first tooth at six months, walked and talked at 14 months. He has had measles and scarlet fever. Mantoux negative.

Physical examination corroborated the roentgenographic findings. The cardiac dullness and impulses were on the right side, and the liver dullness on the left. There was no evidence of any pathologic cause for the dextrocardia on either roentgenographic or physical examination. Electrocardiogram showed mirror image inversion of normal Lead I (figures 1 and 2).

Diagnosis Congenital dextrocardia with situs inversus.

Comment The occurrence of cardiac misplacement in conjunction with transposition of viscera has long been known. The first reported observation is credited to Petrus Servius² in Rome in 1643. It was also reported in Paris in 1650² in the man who was executed for the murder of the Duke of Beaufort, as related by Guy Patin, and later reported in London in 1674. Its incidence has been variously estimated. It is said to be approximately 1 in 10,000. The difficulty in determining the incidence accurately is obvious. However, one case in over 11,000 is here reported. Moffet and Neuhoﬀ³ reviewed the literature from the year 1649 to 1915 and were able to find only 126 reported cases of true congenital dextrocardia.

A second case of congenital dextrocardia with situs inversus was found

* Received for publication August 10, 1935.



FIG 1 Case 1 A Z, male, aged 8 years Congenital dextrocardia with situs inversus

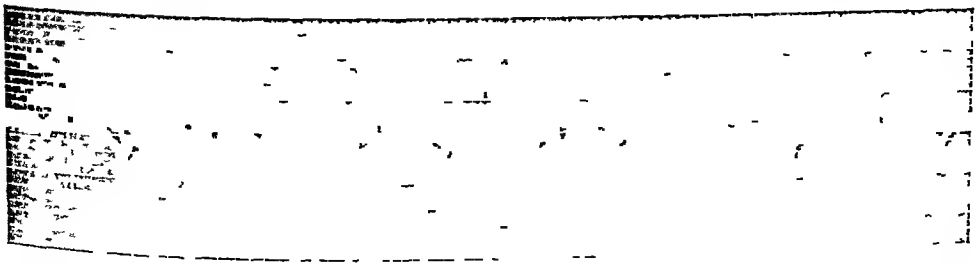


Fig 2 Case 1 A Z, male, aged 8 years Mirror image inversion of normal Lead I

in a child referred to our chest clinic (Pediatric Department, New York Post Graduate Medical School and Hospital)

Case 2 P. M., female, aged 2½ years The chief complaint was of a chronic cough since birth and of frequent colds

Physical Findings 1 Dextrocardia, heart sounds normal, no symptoms referable to the heart 2 Numerous coarse and fine râles on inspiration on both sides posteriorly with some expiratory coarse râles 3 Throat congested, marked post-nasal drip, tonsils enlarged and infected

Laboratory Findings Roentgen-ray Chest 1 Dextrocardia with visceral transposition 2 Central pneumonic infiltration Sinuses Pansinusitis Mantoux Negative Electrocardiogram Mirror image inversion of normal Lead I

Diagnosis 1 Chronic bronchitis 2 Central pneumonitis 3 Pansinusitis 4 Congenital mirror picture dextrocardia with situs inversus

Comment As early as 1749 dextrocardia was divided into congenital and acquired groups Nagel⁴ divided the congenital dextrocardias into two main groups 1 True mirror picture congenital dextrocardia, 2 congenital dextrocardia due to arrest of development

The exact nature of the pathogenesis of these groups is still not clearly understood

In true mirror picture dextrocardia the heart is reversed or transposed upon itself, coming to lie on the right side with the relationship of the various structures of the heart to each other remaining both physiologically and anatomically unchanged The apex points to the right The apex beat is palpated near the right mammary line and is formed by what is normally the left ventricle, presenting a true mirror picture of the heart This type of dextrocardia is usually associated with transposition of the other organs or viscera Congenital mirror picture dextrocardia without transposition of the other viscera (isolated dextrocardia) does occur, but it is exceedingly rare, in which event it is to be differentiated from dextrocardia due to arrest of development It is possible to have all kinds of combinations of transposition of the viscera Abernethy⁵ in 1793 reported the case of a female infant, 10 months of age, in which the heart was on the right side, the liver in the midline with the rest of the organs in their normal positions Royer and Wilson⁶ report the case of a boy, aged six years, found to have complete transposition of all viscera except the heart which was in its normal position Even the lungs were included in the transposition The three-lobed lung was on the left side and the two-lobed on the right

In congenital dextrocardia due to arrest of development the heart is said to retain the position occupied by it during the early stages of embryonic life, because of an arrest of development There is no transposition of other viscera The apex points downward and is formed by the right ventricle As a result of this arrest of development there is not only a dextrocardia but also grave and complex anomalies of the heart associated with it, such as transposition of the aorta and pulmonary artery and complete

defect of the cardiac septa, as in Wenner's ⁷ case. There may be many possible combinations of defects, from the slightest to the gravest, either of the large vessels themselves, of the communication between the large vessels and the heart, or of the heart itself. In this type there is usually marked cyanosis, and the prognosis is grave. In uncomplicated mirror picture dextrocardia the sounds are normal, there is no cyanosis or anatomical interference with the heart function, and the electrocardiogram will show the characteristic findings—a mirror image inversion of normal Lead I. On the other hand in dextrocardia due to arrest of development there is only a right sided preponderance.

Case 3 W F, male, aged 10 years

Past History Normal delivery, cyanosis since birth, feeding was difficult. Mother says that as an infant he turned very blue whenever he cried or ate. Had seven attacks of purulent otitis media in the first year of life and was considered "delicate." Mother was told at three months of age that child had a dextrocardia, and at five years of age was told that he had a murmur in addition to the dextro-

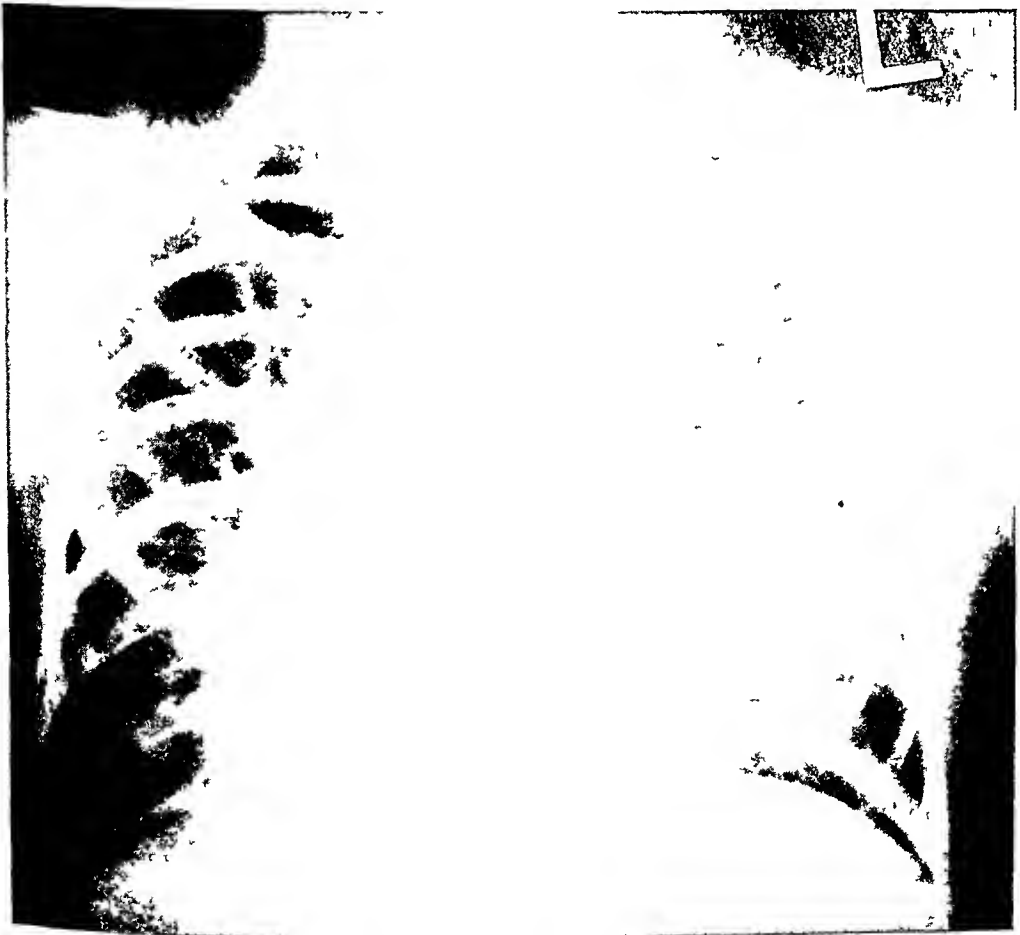


FIG 3 *Case 3* W F, male, aged 10 years. Congenital picture dextrocardia with situs inversus. Congenital heart disease, probably septal defect.

cardia Had bronchopneumonia at seven years of age, which was associated with marked cyanosis Measles at eight years, no complications In February 1935 had left lower lobar pneumonia Temperature seldom reached 101° by rectum, and pulse was between 50 and 60 There was marked cyanosis, and resolution was delayed A month later he had a second attack of pneumonia

Physical Examination Underdeveloped, pale youngster Cyanosis of lips and fingertips, no clubbing Heart impulse felt 11 cm to the right of the midline There was a harsh systolic murmur heard at the base and over the precardium There was no thrill Lungs were clear Liver and spleen not palpable

Fluoroscopic Examination A P View Heart seen to the right of the midline with general cardiac enlargement First Oblique (right shoulder to screen) showed enlargement of left ventricle Second Oblique (left shoulder to screen) showed the retro-cardiac space clear

Roentgen-ray (figure 3) revealed 1 Dextrocardia with situs inversus 2 Enlarged and ovoid type of heart 3 Accentuated pulmonary markings

Electrocardiogram 1 Normal sinus rhythm 2 Normal A V conduction time with occasional sino-auricular block 3 Right axis deviation of the Q R S 4 Q R S low voltage and notched 5 Mirror image inversion of normal Lead I 6 P-wave inverted in all three leads 7 Abnormal T-wave in Lead I Conclusion In addition to a mirror picture dextrocardia these abnormalities indicate myocardial disease with probably some disturbance of conduction through the bundle of His, as indicated by number 4

Diagnosis 1 Congenital dextrocardia with situs inversus 2 Congenital heart disease, probably some septal defect with cardiac enlargement 3 Myocardial disease in region of the bundle of His

Comment The roentgen-ray and the electrocardiogram undoubtedly prove that the dextrocardia is of the true mirror picture type If this case were seen in the first month of life it would be apt to be confused with dextrocardia due to an arrest of development because of the marked cyanosis The roentgen-ray alone would be sufficient to aid in differentiation in that it would reveal the situs inversus which is always associated with true mirror picture dextrocardia The congenital heart lesion (septal defect) which is superimposed upon a true congenital dextrocardia easily accounts for the cyanosis The patient also has myocardial degeneration probably involving the bundle of His, as shown by the electrocardiogram, which may account for the very slow pulse during his attack of pneumonia Moffet and Neuhoﬀ² report a true congenital dextrocardia with situs inversus also associated with a patent inter-ventricular septum with cyanosis

The classification of congenital dextrocardia is not sufficiently inclusive from a practical standpoint This is exemplified in the following two cases which are undoubtedly congenital but have all the characteristics of the acquired type

Case 4 M R male, aged 6 years (of the tuberculosis research group), was referred for physical examination because the heart was found on the right side There were no complaints, except for an occasional cough The appetite was good The delivery was by Caesarian section, and the birth weight was eight pounds Development was normal both physiologically and physically He had measles, scarlet fever and whooping cough There were no subjective symptoms referable

to the dextrocardia or to the condition causing it. Roentgen-ray (figure 4) revealed a definite diaphragmatic eventration with a dextrocardia.

Physical Examination The apex impulse was in the right mammary line with the cardiac dullness on the right side. There was no evidence of transposition of other viscera. Normal liver dullness was elicited on the right side. There was definite increase in resonance with diminished respiratory sounds at the left base. Both child and parents were uncooperative. They disappeared when a fluoroscopy with barium was prepared and repeatedly broke appointments for both a fluoroscopic and electrocardiographic examination. Mantoux test was positive.

Diagnosis Dextrocardia secondary to eventration of diaphragm.

Comment Baynes-Jones⁸ tabulated 45 cases of eventration of the diaphragm from the literature. The great majority occurred in males. Three



FIG 4 Case 4 M R, male, aged 6 years. Dextrocardia secondary to eventration of the diaphragm.

were right-sided lesions, while 42 were on the left side. He states "In eventration the diaphragm is greatly thinned as well as distended, and there is no solution of its continuity. In this essential respect the condition is different from hernia of the diaphragm which, whether true or false depending upon the presence or absence of the hernial sac, consists of a localized opening in the sheet of the diaphragm through which the abdominal viscera pass into the thoracic cavity."

Blackford and Booth⁹ in 1932 reported a case of dextrocardia secondary to eventration of the diaphragm identical to the one here reported. The electrocardiogram was normal. Landis¹⁰ says concerning eventration "That eventration is a congenital abnormality is apparent. As the condition is congenital both the thoracic and abdominal viscera accommodate themselves to the defect, and as a result there are no symptoms." That the condition is not always congenital, however, is evidenced by Hedblom's¹¹ case of dextrocardia secondary to eventration of the diaphragm presumably due to neuritis of the phrenic nerve with evidence of neuritis elsewhere in the extremities. Both the diaphragm and the heart eventually resumed their normal position. Landis further states "The condition may be suspected on physical examination, but in most instances it is discovered as a result of the roentgen-ray examination or at the autopsy table." Of physical signs he says "In left-sided cases the most striking sign is the abnormally large area of tympany both anteriorly and posteriorly. Owing to the large area of tympany the condition most likely to simulate eventration is pneumothorax or congenital hernia. Among the more unusual conditions are large basal cavity and subphrenic abscess producing gas. As eventration never gives rise to any disturbance and is usually an accidental discovery it requires no treatment." Although eventration is considered a harmless condition it may, however, have very serious consequences. Blackford and Booth⁹ quote a case that ended fatally. A young woman had been healthy until several months' pregnant. In the examination because of the abdominal symptoms which developed at that time it was found that she had an eventration on the left side with the heart displaced to the right. She would not consent to an abortion, and during labor which was premature a complete rupture of the diaphragm and death occurred. It is conceivable, therefore, that any condition, such as whooping cough, which could produce a marked increase in intra-abdominal pressure might cause a rupture of the weakened diaphragm. Similarly it is possible that eventration may also be acquired from a congenitally weak diaphragm.

Case 5 L. D., colored female, aged 1½ years, admitted 9/10/34 on Pediatric Service Jamaica Hospital. Died 9/11/34.

Past History Patient well until day before admission when she refused nourishment and vomited the little she took. No bowel movement in the last 36 hours. Two enemas given daily before admission. First yielded some fecal material, second returned clear. Has vomited all food taken day of admission. There was no fever. She received nothing but water in the 24 hours prior to admission. Later additional his-

tory revealed that only liquid food was given the child since birth, and that just prior to the onset the child was given ham and eggs

Physical examination revealed 1 Acetone odor to breath 2 Malnutrition 3 Heart sounds and impulses on the right side 4 Some diminution of breath sounds on the left side with dullness on percussion in the lower part of the chest 5 Marked distention with dullness on percussion over upper left quadrant Remainder of abdomen not distended A nasal tube was passed and 17 ounces of clear fluid were obtained following which distention disappeared 6 Albuminuria 7 Leukocytosis of 15,600 with 74 per cent polynuclear cells



FIG 5 Case 5 L D, female, colored, aged $1\frac{1}{2}$ years Dextrocardia secondary to congenital diaphragmatic hernia

Roentgenogram (flat plate of abdomen and chest) (figure 5) 1 Dextrocardia 2 Hernia of left diaphragm

Diagnosis Congenital diaphragmatic hernia with secondary dextrocardia

The general condition of the child became rapidly worse. It was decided to operate without delay. At operation the stomach was found to be rotated about one inch proximal to the pylorus. The stomach was greatly distended and displaced

upward into the left thoracic cavity together with the transverse colon, spleen and coils of small intestine. The diaphragm was totally absent on left side, there being only reflections of peritoneum about one-half inch wide on either side with some muscular fibers around central dome. The child died several hours after the operation.

Autopsy corroborated the operative findings. 1 Massive collapse of left lung 2 Displacement of heart to the right 3 Fatty degeneration of liver 4 Herniation of left diaphragm 5 Repair of left diaphragmatic leaf

This is undoubtedly a congenital hernia (false) because of the almost complete absence of the diaphragm, the absence of a history of violent injury, and evidence that the collapse of the lung had existed for a long period.

Comment. Diaphragmatic hernias are classified either as congenital or acquired, and are further classified as true or false depending upon the presence or absence of a sac. The congenital hernia is due to incomplete development of the diaphragm. The acquired hernia develops after birth in a congenitally weak area similar to the development of a hernia elsewhere and obviously has a sac except those of traumatic origin due to violent injury, gunshot and stab wounds.

The signs of hernia are varied and inconstant. The first symptom may be manifest soon after birth and be either respiratory or gastrointestinal, or it may develop in later life, as in this child, with symptoms of obstruction which were produced by torsion of the stomach above the pylorus. One must appreciate the various possible signs that could be produced by the stomach filled with air or fluid, the large and small intestines and possibly the spleen, all or part of which may be in the chest cavity, most commonly on the left side. The symptoms may include any combination of the following: cough, dyspnea, cyanosis, decreased respiratory movement on the affected side, bulging of the chest, absence of respiratory murmur and signs of either fluid or pneumothorax. The abdominal signs may be vomiting, nausea, unusually flattened abdomen and signs of obstruction. A dextrocardia should always stimulate a search for diaphragmatic hernias since these are frequently the cause of displacement of the heart to the right side. Following successful repair of the hernia the heart returns to its normal position.

The most important and difficult differentiation to make is that between diaphragmatic hernia and eventration. According to Giffin¹³ the term eventration was first used by Petit in 1790 and applied to the condition of chronic idiopathic unilateral elevation of the diaphragm. He considers it a most unsatisfactory term. Eventration is defined as "protrusion of the bowels through an opening in the abdominal wall." Hernia is defined as "the protrusion of an organ or part of an organ or other structure through the wall of a cavity normally containing it." Giffin feels that the terms might easily be interchanged and perhaps rightly so. Since all true hernias must have a sac and since most congenital diaphragmatic hernias and those acquired of traumatic origin have no sac, it would not only be more descriptive but also anatomically correct were the terms to be reversed.

There has been a marked increase in the cases diagnosed and reported in recent years. This is due chiefly to the advance in roentgenologic diagnosis.

The diagnosis rests chiefly and finally on roentgenologic examination. Some hernias are spontaneously reduced in the upright position. Hence, if there is any doubt as to the diagnosis it is advisable to make the roentgenologic examination in either the horizontal or Trendelenburg position. Once the diagnosis is made, surgical intervention should follow, because the mortality is much higher in complicated cases such as the one above reported. The operative mortality has been greatly reduced in recent years. Hedblom¹⁴ states that among 57 cases reported during the last three years the immediate result was good in 72 per cent. There were eight deaths, a mortality of 14 per cent.

This type of dextrocardia is not generally included in the classification of congenital dextrocardias. Dextrocardia secondary to congenital diaphragmatic eventration or hernia is obviously congenital, but it is caused by pathologic conditions similar or identical in principle to the dextrocardias of acquired origin. Since the term congenital merely means to be born with, I think it is preferable that this type of case be classified as "congenital dextrocardia with acquired characteristics." Paradoxical as it may appear I feel that it is quite descriptive. Jones¹⁵ gives a similar classification for this group. By dextrocardia of acquired origin is meant a heart which has been displaced to the right from the normal left-sided position which it had occupied, by some pathological process.

The following cases illustrate the acquired type.

Case 6 M. M., colored female, aged 10 years (of the tuberculosis research group), was referred for physical examination because of marked disease in the right lung and a dextrocardia. On inquiring whether there were any complaints we were told "just pain in the chest" and "hoarseness."

Family History Father and mother in good health. Five children, none dead, no history of tuberculosis in the family.

Past History Normal birth, no asphyxia or cyanosis, normal development, first tooth at five months, walked at nine months and talked at one year. Had measles and whooping cough. The mother stated that the child had no respiratory trouble.

Physical Examination Malnourished in appearance, enlarged cervical lymph nodes, foul breath, tonsils large, cryptic, almost meet in the midline. Chest is narrow, asymmetrical, right chest is smaller and retracted, marked Harrison's groove, impairment of resonance over whole right chest with fine and large moist râles scattered throughout, particularly the upper half. The breath sounds increased on the right side. There was a hyperresonant note on the left side. The apex beat was on the right side near the nipple line in the fourth interspace about 5 cm. from the mid-sternal line. Four tuberculin tests (Mantoux) with increasing strengths were negative (the strongest dilution being 1-10).

Electrocardiogram 1 Normal sinus rhythm. 2 Normal A-V conduction time. 3 Neither right nor left axis deviation.

Fluoroscopic examination corroborated the roentgenographic (figure 6) findings of dextrocardia and marked right-sided pulmonary disease. There was retraction of the right chest with diminished respiratory movements. Bands of pleuro-pericardial adhesions were distinctly visible which were undoubtedly binding the heart to the right side.

Diagnosis Non-tuberculous fibrosis of the right lung with pleuro-pericardial adhesions causing dextrocardia.



FIG 6 *Case 6* M M, female, colored, aged 10 years (May 1, 1933) Dextrocardia secondary to pulmonary infiltration and pleuro-pericardial adhesions with emphysema of the left side

It was difficult at the time definitely to rule out a pneumothorax. The absence of the retracted visceral pleural line that is seen in pneumothorax, the findings on fluoroscopy, particularly the pleuro-pericardial adhesions, the persistence of the dextrocardia to date since first noted in May 1933 (patient was reexamined in April 1934, and dextrocardia was still present but with somewhat diminished pulmonary infiltration on the right side) and the subsequent course leave little doubt as to the diagnosis. On November 19, 1934, she was admitted to the children's ward in Jamaica Hospital with an extensive bronchopneumonia on the left side and dextrocardia. After the bronchopneumonia had subsided the dextrocardia still persisted. At this time the child was again fluoroscoped, and the pleuro-pericardial adhesions were visible on the right side.

The following case of dextrocardia in an adult was similar to but much

more advanced than the case just reported, and the report of autopsy is available *

Case 7 L. G., male, aged 42 years Admitted Dec 9, 1932, died Dec 28, 1932
Chief complaint Dyspnea and orthopnea

Present Illness Hacking cough, productive, started two weeks ago Had similar attack two and one-half years ago During recent attack feet were swollen The swelling decreased when he stayed in bed

Past History About 12 years ago patient first noticed that he became short of breath and about that time developed a cough, at first dry but later productive

Physical Examination On admission temperature 99.8° F, pulse 96, and respirations 30 The patient is a well nourished adult male, perspiring and coughing persistently, forcefully and productively

Chest Impairment of resonance on right side with increased vocal and tactile fremitus along entire right side anteriorly and posteriorly There are numerous crackling râles at the right base Heart Maximum impulse felt in the third right interspace 8 cm from mid-sternal line First sound moderately loud and short Faint systolic blow and short presystolic murmur

Röntgen-ray diagnosis 1 Dextrocardia 2 Chronic infiltrative process in the right lung with retraction of chest wall and displacement of the trachea 3 Small exudate in right chest 4 Chronic bronchitis and bronchiectasis of left lung

Electrocardiogram Normal rhythm No mirror inversion image in Lead I Left axis deviation of the QRS T₁ and T₂ are diphasic There are premature ventricular beats in Leads II and III

Clinical conclusion Ventricular myocardial disease

Patient became progressively worse with a rising temperature and died Dec 28, 1932

Summary of autopsy findings 1 Non-tuberculous fibrosis of right lung, incident to old interstitial pneumonia with pleuro-pericardial adhesions, compensatory enlargement of left lung with minimal apical fibrosis, diffuse suppurative bronchitis and bronchopneumonia 2 Dextrocardia with cardiac hypertrophy and dilatation 3 Cirrhosis of spleen and kidneys 4 Chronic passive congestion of spleen and kidneys 5 Supernumerary nipple

Cause of death Bronchopneumonia

Diagnosis Dextrocardia secondary to non-tuberculous fibrosis of the right lung and pleuro-pericardial adhesions

Comment I have added this adult case, not only because of its autopsy findings, but also by way of complement to the preceding case of M. M., aged 10 years, also with dextrocardia, pleuro-pericardial adhesions and pulmonary infiltration It pictures to us the probable outcome of the child in the not too distant future In both cases there was considerable compensatory emphysema of the left lung It is difficult to say how much of the cardiac displacement is due to the emphysema It is easily conceivable that it does exert some force If that is so, then there are two distinct forces exerted in the same direction in displacing the heart to produce the above type of dextrocardia, fibrosis of the lung with fibrous bands causing traction, or a pulling force on the heart, and an emphysema pushing the heart to the right

* This case was on the service of Dr. Carl Boettiger, at the Mary Immaculate Hospital, Jamaica, to whom I am indebted for permission to report it

Case 8 G W, male, aged 21 months

Past History Irrelevant

Present Illness Ill for about one week prior to admission to hospital January 22, 1935, at which time he was extremely ill, cyanotic, dyspneic. Temperature 100°. Evidence of consolidation of the left lower lobe. Five days after admission showed evidence of fluid in the left chest. Fluid increased very rapidly with evidence of cardiac displacement to the right. Paracentesis performed and pus was removed from the left chest. Roentgen-ray revealed evidence of a great deal of fluid in the left chest with considerable displacement of the heart and trachea to the right. Child was operated upon immediately for empyema, made a good recovery, and heart returned to its normal position.

Diagnosis Dextrocardia secondary to empyema on the left side

Comment The causes of acquired dextrocardia are many. Any condition which can cause displacement of the heart to the right side can produce a dextrocardia. In its normal position approximately two-thirds of the heart lies to the left. Obviously there may be various degrees of dextrocardia from partial to complete. Among the numerous conditions reported causing dextrocardia are: On the right side—tuberculous fibrosis, non-tuberculous fibrosis, pleuro-pericardial adhesions, atelectasis and carcinoma. (In 16 cases of acquired dextrocardia reported by Hedblom¹¹ three were due to carcinoma of the right lung.) On the left side—diaphragmatic hernia and eventration, tumor or cysts of the lung, fluid in left chest and pneumothorax. Miscellaneous causes include scoliosis, megacolon and mediastinal emphysema. The symptoms naturally are dependent upon the underlying cause.

SUMMARY

Eight cases of dextrocardia are reported, three of which were discovered in a series of 11,253 roentgen-rays of children's chests. These eight cases were as follows:

- 1 A true mirror picture dextrocardia with situs inversus
- 2 Dextrocardia secondary to congenital eventration of the diaphragm
- 3 Acquired dextrocardia secondary to pleuro-pericardial adhesions with non-tuberculous infiltration of the right lung
- 4 and 5 Two additional cases of true congenital mirror picture dextrocardia, one of which was associated with a patent interventricular septum, cyanosis and myocardial disease involving the bundle of His
- 6 Dextrocardia secondary to congenital diaphragmatic hernia
- 7 Dextrocardia secondary to non-tuberculous fibrosis and pleuro-pericardial adhesions in an adult with autopsy findings
- 8 Dextrocardia secondary to empyema on the left side

A modified classification of dextrocardia is proposed

I CONGENITAL

- 1 True mirror picture dextrocardia (A) with situs inversus, (B) isolated congenital dextrocardia without situs inversus
- 2 Dextrocardia due to arrest of development

- 3 Congenital dextrocardia with acquired characteristics, as that secondary to congenital diaphragmatic hernia, eventration or atelectasis

II ACQUIRED

- 1 Dextrocardia developing after birth secondary to acquired conditions

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THE LETHAL EFFECTS OF SOLAR RADIATION ON GUINEA PIGS

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DURING the last 15 years, a few reports have appeared in the literature in which it was stated that mammals, and particularly rodents, died sometimes when exposed to solar radiation for relatively short periods of time. That radiant energy in certain parts of the spectrum may be lethal for photosensitized animals is well known, but it is interesting to note that several authors were surprised when they observed the lethality of solar insolation for nonsensitized animals. The hitherto published work is based on essentially qualitative studies, none satisfied even elementary physical considerations. There are no adequate measurements of the power γ of the radiant energy that is lethal under the conditions of the particular experimental situation, nor are there any measurements of the spectral distribution of the radiant energy incident upon the test animals. Furthermore there are only totally inadequate attempts to determine the potential dependence of the phenomenon upon variations of the spectral composition of the incident energy. The descriptions of the pathological changes in the test animals are incomplete and controversial.

We stumbled on the observation that guinea-pigs were sensitive to radiant energy and that they died regularly within an hour when exposed to the midday sun at Tucson, Arizona (altitude 2,600 feet, latitude $32^{\circ} 15'$ North), even at the time of the winter solstice. Since bibliographical search showed us that this phenomenon was little known, that the observed data were inadequate and that the conclusions drawn from them were often erroneous and misleading, we decided to study this condition. Our decision was encouraged by two considerations: (1) that in the Research Institute of the Desert Sanatorium in Tucson we had at our disposal physical apparatus and meteorological conditions suited for such experimental studies, and (2) the thought that the physiological effects of absorbed radiant energy could be studied to best advantage under conditions in which the observable *status quo* is not maintained, i.e., in which physiological compensation is inadequate, rather than the reverse, for complete compensation often obscures the changes initiated by the stimulus. Therefore, the apparent sensitivity of rodents to powers of radiant energy seemed a fertile object for the study of physiological effects produced by this form of energy.

* Presented at the Detroit meeting of the American College of Physicians, March 6 1936.

From the Laboratories of the Desert Sanatorium and Institute of Research, Tucson, Arizona.

γ The term power is used in this paper in its correct physical sense, meaning "rate of flow of energy, i.e. $\text{Power} = \frac{\text{Energy}}{\text{Time}}$."

The experimental apparatus consisted of a Foucault siderostat, carrying a 12-inch square stellite mirror mounted in a dome connected by a passageway with a windowless room free of drafts. The radiant energy of the sun is reflected by such a siderostat in a constant direction, in this instance into the adjoining room, regardless of the changing altitude and azimuth of the sun. The radiation was passed through a 12-inch fused quartz lens of approximately two meter focal length. The shaved ventral surfaces of the guinea pigs were exposed at right angles to the beam through a slit of constant dimensions (2" by 4"). A thermocouple was mounted in the plane of the animal and was connected with a galvanometer of suitable characteristics. The deflections of the latter in response to radiant energy incident upon the receiving surface of the thermocouple had been calibrated for conversion into absolute energy units. Variation in the power of the incident energy was obtained by translational movement of the animal toward or away from the focal point of the quartz lens. Fractionation of the spectrum was accomplished by the interposition in the beam of solar radiant energy of suitable quartz, glass, and liquid filters whose transmission characteristics had been determined by standard spectrometric methods.

Over 100 animals were exposed to various powers of radiant energy of the following spectral compositions

- (a) 0.30μ – 3.0μ (integrated solar radiant energy at Tucson) (34 animals)
- (b) 0.30μ – 1.4μ (integrated solar radiant energy minus "far infra-red") (11 animals)
- (c) 0.37μ – 3.0μ (integrated solar radiant energy minus "ultra-violet") (14 animals)
- (d) 0.37μ – 1.4μ (integrated solar radiant energy minus "far infra-red" and "ultra-violet") (6 animals)
- (e) 0.34μ – 0.66μ (practically only "visible") (24 animals)
- (f) 0.62μ – 3.0μ (practically only "near" and "far infra-red") (11 animals)
- (g) 0.62μ – 1.4μ (practically only "near infra-red") (14 animals)
- (h) 1.0μ – 15.0μ (practically only "far infra-red") (9 animals)—(Artificial source of radiant energy used in this instance)

In each of the above spectral regions, we determined (with due consideration of such variables as body weight, room and body temperature and skin pigmentation) the minimal powers of radiant energy to which the animals regularly succumbed within one hour, they are approximately of the magnitude of those of unconcentrated solar radiation at Tucson. These figures were then corrected for losses by reflection at the surface of the animal. The detailed data will be published elsewhere. Here we wish to report only that *each of the above arbitrary divisions of the solar spectrum can be lethal for guinea pigs* and to describe the clinical and pathological findings, which were remarkably uniform and which, with the exception of

minor details, appeared to be *invariant under variation in spectral composition of the radiant energy to which the animals were exposed*

Under experimental conditions such that death occurs in about one hour, the respiratory rate usually begins to accelerate within 10 minutes after the onset of the exposure, and often attains rates in excess of 180 per minute within 30 or 40 minutes, then the respiration drops suddenly to less than the normal rate and becomes markedly irregular and grunting. The impression was gained that during the last few minutes of life, there develops a discoordination of the respiratory musculature, in the sense that inspiratory and expiratory muscles contract simultaneously. The animals die usually within 10 or 15 minutes following the drop in their respiratory rate.

The rectal temperatures rise rapidly to 108° F or more, usually within 45 minutes. At the time of death the rectal temperature is, in most animals, above 110° F. When the exposure was interrupted after the animal had reached 108° or 109° F, the temperature dropped to normal within less than an hour, and often subsequently to subnormal figures, but the animal died, as a rule, within the next 12 or 24 hours.

In animals that died during the exposure, that is within one hour, or shortly afterwards, the gross autoptic findings were quite uniform throughout. The exposed portions of the skin showed numerous petechiae, the subcutaneous tissues were edematous and congested. The lungs showed areas of massive congestion irregularly scattered throughout the parenchyma, apparently unrelated to the posture of the animal during the exposure. A few animals had a slight amount of free blood in the pleural cavities. The left heart was maximally contracted, the right heart was maximally dilated, a finding characteristic of peripheral vascular paralysis. The liver was diffusely congested, and the gall-bladder was always distended with clear bile if the animal had died during the exposure, but when death was delayed for 10 minutes or more the gall-bladder was found empty. The spleen was moderately or markedly congested, and all the splanchnic vessels were distended with blood. Loops of the intestines and part of the anterior gastric wall directly beneath the abdominal wall had patchy areas of hemorrhagic discoloration and edema, and in some animals there was evidence of hemorrhagic infarction in these areas. The kidneys and adrenals showed varying degrees of congestion. The brain showed no abnormality.

Histological studies revealed a number of different lesions in the lungs, namely (1) massive capillary hyperemia, (2) capillary intraalveolar hemorrhages, (3) small areas of predominantly interstitial lobular pneumonias whose exudate consisted of histiocytes, polymorphonuclears and red cells, (4) scattered, chiefly subpleural, areas of emphysema, (5) markedly contracted bronchial musculature, (6) desquamation of bronchial epithelium, and (7) edema and lymph stasis in the septa. In the involved areas of the gastrointestinal tract, we found simple hyperemia, particularly in the submucosa, massive edema of the same layer, capillary stasis, hemorrhagic in-

fractions and localized complete necroses. Sections through the exposed portions of the abdominal wall showed small cutaneous extravasations, massive subcutaneous edema and, in cases of delayed death, degenerative changes in the superficial layer of muscle fibers. The other organs showed no pathological changes, with the exception of marked congestion.

DISCUSSION

As was mentioned before, previous reports on the lethal effect of radiant energy on mammals both in regard to its physical foundation and to its pathological results are incomplete. In no instance was there measurement by standard physical methods of the power of the radiant energy incident upon the experimental animal. A few authors recorded and reported the readings of mercury in glass-thermometers, the bulbs of which were exposed to the radiant energy incident upon the test animal. Such readings are not at all an absolute measure of the incident radiant energy, but merely represent the equilibrium temperature attained by the glass bulb of the thermometer in contact with the air surrounding it, which in turn depends upon the fractions of the incident energy that are absorbed by the glass bulb and by the air, which vary with the wave-length as well as with the power of the incident energy. For equal powers of radiant energy, a mercury-in-glass-thermometer gives different readings in different parts of the spectrum in which its absorptivity differs. Since no author recorded in absolute units the powers of the radiant energy to which they exposed their animals, their results cannot be compared. If, as was reported in several instances, the results of experiments with artificial sources of radiant energy did not agree with those with solar insolation, that can only mean that in the one instance the flow of radiant energy did, and in the other did not, exceed that rate for which the test animal under the conditions of the experiment could compensate. For, a logical analysis makes it clear that in any given set of conditions, *there must be some rate of flow of incident energy which no animal can survive indefinitely*. No system which is not in energy equilibrium with its environment can maintain its status quo, i.e., a change of state must occur. Since there are physiological limits to the rate at which a given animal can dissipate energy, the problem resolves itself into the determination of that power of incident radiant energy for which the test animal can compensate by an adequate dissipation of energy. If energy intake is continuously greater than energy output, death must eventually occur.

The surprising thing is that the power of unconcentrated solar radiant energy at many places on the earth's surface is of such an order that the compensatory physiological mechanisms of rodents cannot cope with it, not even for relatively short periods of time.

No author has reported or apparently measured the spectral distribution of the radiant energy to which he subjected his experimental animals, in

tact, several used identical sources, but fixed their attention on one zone of the spectrum while disregarding others present. For instance, some authors used the mercury-vapor-lamp as a source rich in "ultra-violet," while others used the same instrument as a source rich in "visible light"—both neglecting the fact that as much as 40 per cent of the total energy of an average mercury-vapor-lamp may be emitted as radiant in wave-lengths longer than $8,000 \text{ \AA}$ (i.e., "infra-red")

One of the main points of discussion in the literature is the question whether the lethal effect of irradiation is due to the "thermic rays," the "light rays" or the "actinic rays." These terms are both ambiguous and misleading. Ambiguous, because they do not denote well defined spectral regions, but only approximate ones. Misleading, because radiant energy is neither "thermic" nor "luminous" nor "actinic" until it is absorbed; whether a given quality and quantity of radiant energy upon absorption will (a) increase the average kinetic energy of the absorbing molecules (i.e., raise the temperature of the absorbing substance), (b) be perceived as light if it falls on the retina, or (c) disrupt molecules (i.e., initiate a chemical change) is *dependent upon the characteristics of the absorbing medium as well as that of the radiant energy*. The term "light" should be restricted to the sensation resulting from stimulation of the retina. For example, if radiant energy of say $4,500 \text{ \AA}$ wave-length falls upon the retina, a sensation of light is experienced, if it falls upon a photographic plate, a chemical change is initiated, and finally if it is directed upon a layer of platinum black, a rise in temperature will ensue, i.e., appear as heat. It remains to be discovered what the response of the skin is to radiant energy of different wave-lengths, but the fortuitous differentiation of the spectrum dependent upon a specialized end-organ, such as the retina, should not be superimposed on other receptors, such as the skin. If the radiant energy of wave-length $6,000 \text{ \AA}$ stimulates the retina, and $8,500 \text{ \AA}$ does not, it does not follow that these spectral regions will produce dissimilar effects in the skin. Whether they do or do not, remains to be determined, and should not be prejudged by labels such as "heat" and "light." Since it is apparent that there must exist for radiant energy of any wave-length *that is absorbed* in no matter what small percentage, some power of incident energy which the test animal cannot survive indefinitely, the problem is therefore not whether the "light rays" or the "heat rays" or the "actinic rays" can be lethal, but what the minimum lethal power is in the various parts of the spectrum under a given set of experimental conditions. This we have determined and the results will be published elsewhere.

The physiological mechanism by which absorbed radiant energy causes death is still unknown and must, for the present, remain a matter of speculation. All of the authors who observed the lethal effect of radiant energy noted that death was in every instance, accompanied by a hyperthermia often exceeding 110° F . The question therefore arises as to whether death

occurs solely because of the production of a hyperthermia. Our findings can be analyzed to give direction for further study. Although we have confirmed that fever is one of the outstanding manifestations, it is not high enough in all animals to cause death per se. In this connection it might be significant, too, to point out again that under appropriate experimental conditions animals die hours after they have regained their normal temperature. It remains to be determined whether the hyperthermia is due simply to the conversion of radiant energy into heat (i.e., an accumulated energy imbalance) or whether it is due, at least in part to indirect causes, such as the liberation of fever-producing substances in those tissues that absorb the radiant energy, or due to a specific physiological derangement of the temperature regulating mechanism by some action of the absorbed radiant energy.

The morphological findings are suggestive of two sets of action: (1) one that is limited to the regions in which radiant energy is undoubtedly absorbed, such as the exposed skin, the underlying subcutaneous tissue and muscle fibers and, apparently the gastric and intestinal walls adjacent to the abdominal wall, and (2) one that is apparently independent of the localization of the incident energy. The direct action is an intense inflammatory stimulus whose initial effect is a marked increase of the permeability of capillaries, for in the regions of direct action we find edema, blood stasis and its sequences all the way to infarction and necrosis. The medium by which the indirect action is conveyed is unknown. Since the skin is undoubtedly severely injured, since the pathological picture is that of generalized vascular paralysis, with practically universal arteriolar and capillary dilatation, since the lungs show patchy emphysema and contraction of bronchial musculature, it is inviting to ascribe the indirect effects to histamine-like substances that may be liberated in the regions of direct action. This is, as yet, no more than a speculation which is, however, susceptible of experimental confirmation.

The most surprising morphological finding is the occurrence of pneumonic lesions in the lungs, these have not been previously recorded. Although it can never be proved that they did not antecede the exposure, we can state definitely that they were present in the majority of all animals killed by radiant energy and that they were absent in all control animals, including those that were treated in exactly the same way as the test animals, except that they were not irradiated. The conclusion seems, therefore, inescapable that they were caused by the absorbed radiant energy. Since these pneumonic lesions were found in animals whose abdomens only were irradiated, they must probably be ascribed to the indirect effects.

Conclusions applicable to man must be drawn with great caution from these experiments, because man has vastly more efficient compensatory mechanisms than has the guinea-pig. The latter has practically no sweat glands; its normal respiratory rate is relatively high so that increased dissipation

pation of heat by increased respiration is quite limited, furthermore its skin is very thin so that radiant energy penetrates probably relatively deeper

On the other hand it is apparent that the initial tissue alterations caused by radiant energy are essentially the same in all mammals

It is probably significant that pulmonary hemorrhages are a constant finding, this may be looked upon as an experimental confirmation of the empirical opinion that insolation may produce hemoptysis in patients with pulmonary lesions. Some of the other findings in our experimental animals bring to mind two clinical conditions in man, namely the so-called "Sonnenbronchitis" of some German authors and the so-called "summer-pneumoniae". But since these two diseases are not generally accepted as clinical entities, and since their pathological substrata are unknown in the first, and not well established in the second disease, we wish only to mention that our findings may possibly have some bearing on these conditions in man.

These studies present, as far as we know, the first experimental proof that radiation in the spectral region $0.34\mu-0.66\mu$ (i.e., almost coinciding with the region called "visible") can produce profound biological effects in non-sensitized animals. In particular, the lethal effect of radiation on mammals in the few instances that have been previously reported, has been uniformly ascribed either to the "ultra-violet" or the "infra-red" portions of the spectrum.

SUMMARY

That mammals, and particularly rodents, may be killed by radiant energy without previous photosensitization, has been observed by a few workers. This phenomenon has, however, never been studied thoroughly, and no attempts have ever been made to measure adequately the incident radiant energy both as regards the minimal lethal power and its spectral distribution.

In experiments that fulfilled these basic physical requirements, the authors have shown

1 Guinea pigs whose shaved abdomen, or thorax, or both is exposed to a sufficient power of solar radiant energy die within one hour with a characteristic sequence of clinical phenomena.

2 The power of radiant energy required for this lethal effect is of the magnitude of solar radiation existing at an altitude of 2,600 feet and a latitude of $32^{\circ} 15'$ North.

3 The spectral regions for which this lethal effect has been proved are as follows

- (a) $0.30\mu-3.0\mu$ (integrated solar radiant energy at Tucson) (34 animals)
- (b) $0.30\mu-1.4\mu$ (integrated solar radiant energy minus "far infra-red")
(11 animals)
- (c) $0.37\mu-3.0\mu$ (integrated solar radiant energy minus "ultra-violet")
(14 animals)

- (d) 0.37μ – 1.4μ (integrated solar radiant energy minus “far infra-red” and “ultra-violet”) (6 animals)
- (e) 0.34μ – 0.66μ (practically only “visible”) (24 animals)
- (f) 0.62μ – 3.0μ (practically only “near” and “far infra-red”) (11 animals)
- (g) 0.62μ – 1.4μ (practically only “near infra-red”) (14 animals)
- (h) 1.0μ – 15.0μ (practically only “far infra-red”) (9 animals)—(Artificial source of radiant energy used in this instance)

4 The pathological findings in the animals that succumbed to the effects of radiant energy are as follows

Massive congestion of lungs, liver, spleen, splanchnic vessels, of those parts of the gastrointestinal canal and of the subcutaneous tissue that lie directly beneath the exposed skin surface, less marked and less constant congestion of kidneys, adrenals and testes. Maximal contraction of the left heart and maximal dilatation of the right heart.

Histologically, small lobular, mainly interstitial pneumonias are frequently seen, associated with these lesions and with irregularly distributed regions of intense capillary congestion, are intraalveolar hemorrhages, patches of mainly subpleural emphysema, contracted bronchi. The intestinal loops and the anterior wall of the stomach show frequently, in addition to massive congestion, stasis, submucous edema, localized hemorrhagic infarctions and necroses.

OCCURRENCE OF MACROCYTIC ANEMIA IN ASSOCIATION WITH LESIONS OF THE BOWEL *

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It is well known that a variety of conditions are often accompanied by a morphologic blood picture resembling, and often indistinguishable from, the blood picture of pernicious anemia. Conspicuous among these conditions are instances in which the intestinal tract is involved in some disease process. This study was undertaken to determine, if possible, just what lesions of the ileum and cecum are likely to be accompanied by an anemia which resembles pernicious anemia.

The first case in which pernicious anemia probably was secondary to an intestinal disturbance was reported by White, in 1890. At necropsy, ulcerative and cicatricial lesions were found in the colon. Faber (1895), according to Strauss, reported the first case in which a blood picture of pernicious anemia apparently was the result of an anatomic abnormality. Two fibrous strictures of the small intestine were found at necropsy. These strictures were probably secondary to a healed tuberculous process. In 1897, Faber reported another case of pernicious anemia which was associated with intestinal obstruction. Since this time blood pictures which are characteristic of pernicious anemia have been reported in cases in which there were various organic abnormalities of the intestinal tract. Seydelhelm, Lehmann, and Wichels (1924) produced a stenosis in the small intestines of dogs, and in two of the 10 animals the blood picture resembled that of pernicious anemia. These same workers (1927) mention a case in which pernicious anemia developed secondary to a stricture of the small intestine. When the stricture was surgically eradicated the blood picture became normal. Little, Zerfas, and Tiusler (1929) reported the development of the blood picture of pernicious anemia in a case in which there was a stricture of the small intestine. The anemia, however, was not relieved when the bowel was restored to its normal state. In a review of the literature, in 1929, Meulengracht found 22 cases in which pernicious anemia apparently was the result of organic abnormalities of the intestinal tract. In 18 of these cases there was a stricture of the small intestines, in three there was a stricture of the colon, and in one there was a stricture of the cecum. Schlesinger (1933) observed a case in which pernicious anemia occurred secondary to intestinal stenosis. In the stomach, however, he still found the intrinsic factor (Castle). This evidence suggested that the pernicious

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anemia was caused by faulty absorption in the intestinal tract. Strauss (1934) mentioned a boy, eight years of age, who had pernicious anemia following the development of numerous short circuits between various loops of small intestine. Strauss also reported a case of pernicious anemia in which the patient was a man who was receiving an adequate diet and whose gastric juice contained the intrinsic factor. The patient, however, had pernicious anemia apparently because he was unable to absorb material necessary for formation of blood, because of multiple intestinal anastomoses.

Miller and Rhoads (1935) have produced macrocytic anemia in swine by feeding them a deficient diet. Achlorhydria, diarrhea, and changes in the bone marrow, which were characteristic of pernicious anemia, also occurred. Remissions could be produced by feeding liver extract. Unpublished work in their laboratories suggested that the lack of an intestinal secretion is not the only important factor. After resection of almost the entire ileum of dogs, the blood picture was only that of a mild hypochromic anemia. These investigators said that "apparently some disorder involving both the stomach and intestine is required to produce the desired results."

Ivy, Richter, Meyer, and Greengard (1934) observed that dogs deprived of their stomachs had a hypochromic anemia that responded to administration of iron. Brown (1934) intimated that pernicious anemia is almost invariably associated with lesions of the gastrointestinal tract.

It would seem that a number of conditions which involve the intestinal tract may, therefore, be accompanied by the blood picture of pernicious anemia.

Hartmann and Pilliet first described hypertrophic intestinal tuberculosis in 1891. The studies by Rubin (1930) indicate that gastrointestinal tuberculosis is common among patients who die of chronic pulmonary tuberculosis. Davis (1933) observed that in 22 of 29 cases of intestinal tuberculosis the involvement was at the ileocecal region. Keefer, Huang and Yang (1929) pointed out that in cases of intestinal tuberculosis the degree of hypochromic anemia was greater in cases in which diarrhea was present than it was in cases in which diarrhea did not occur. However, Brown and Sampson (1930) are among the few writers who have stated that intestinal tuberculosis might produce a blood picture suggestive of pernicious anemia. In such cases, they considered the frequently associated stricture of the small bowel as the possible etiologic factor in the production of this blood picture. No anemia, however, was reported by Masson and McIndoe (1929) or by Counsellor (1929) in their cases of hyperplastic tuberculosis of the ileum.

Regional ileitis, as first described by Crohn, Ginzburg, and Oppenheimer (1932), was supposedly confined to the ileum and was usually accompanied by a moderate progressive anemia. More recently, Harris, Bell, and Brun (1933) and Homans and Hass (1933) have observed that the condition might occur at any point in the intestinal tract. Bissell (1934), Binney (1935), and Mixer (1935) did not mention anemia in their reports but Brown, Bargin, and Weber (1934) observed a mild to a moderate secondary

anemia in 50 per cent of 18 cases of regional ileitis. A review of the literature does not reveal any cases of regional ileitis in which there was a macrocytic type of anemia.

It is well recognized that anemia may be associated with diarrheal diseases which cause little or no hemorrhage. This may, in part, be the result of a deficiency associated with the rapid flow of intestinal contents and a resulting want of absorption in the intestine. Cramer (1923) and Goldblatt and Benischek (1927) found that both vitamins A and B were necessary for the development of the healthy mucous membrane of the intestines and for maintaining its resistance to infection. Tilden and Miller (1930) observed marked changes in the colon and clinical signs of human colitis among monkeys which were fed with diets which were deficient in vitamins. Keefer, Yang and Huang (1929-1931) reported several cases in which chronic dysentery was associated with various types of anemia. The anemia varied in its severity and in its morphologic characteristics. Hyperchromic, hypochromic, macrocytic, and microcytic types of anemia were observed. Even the characteristic clinical features of pernicious anemia were present in some of these cases. In some of the cases the anemia responded to the administration of liver, iron, or a high caloric diet, in some cases the anemia improved after the patients recovered from the dysentery. These authors concluded that the syndrome of pernicious anemia can develop without changes in gastric acidity in cases in which patients have received inadequate diets and have had a pathologic process which interfered with normal nutrition.

We might mention the frequent association of the blood picture of pernicious anemia with other conditions which involve the intestinal tract but which are not considered in this study. Birkeland (1932) in his excellent study on "*Bothriocephalus* anemia" considered in detail the relation between *Diphyllobothrium latum* and pernicious anemia. Logan (1921) reported four cases in which there was infestation with *Balantidium coli*. All of these patients had a blood picture of pernicious anemia and, in addition, had subacute combined sclerosis. Reed and Wyckoff (1926), Baumgartner and Smith (1927), and Castle, Rhoads, Lawson and Payne (1935) have pointed out the similarity between the blood picture of sprue and that of pernicious anemia. Other workers have observed the similarity in the microscopic appearance of the intestine in sprue (Castle, Rhoads, Lawson, and Payne, 1935), intestinal infantilism (Bennett, Hunter, and Vaughan, 1932) and various types of chronic diarrhea (Linder and Harris, 1930). Wills (1934) reported a few cases of tropical macrocytic anemia in which the anemia was distinctly different from pernicious anemia and was not necessarily associated with diarrhea, defective gastric secretion, or pregnancy.

An explanation of the production of the macrocytic anemia that frequently is seen in association with lesions of the intestinal tract has been offered by Castle and his coworkers (1929, 1930, 1931). Castle, Town-

send, and Heath (1930) said "Next to a defect of the original formative process within the stomach, the loss of the absorptive power of the intestinal tract either mechanically or by way of bacterial invasion or the destruction in the bowel of the effective principle after formation would be the most obvious ways in which a deficiency of the final effective substance could be brought out. These remarks indicate that a defect of gastric function alone is not necessarily the only way in which, quite in accord with our hypothesis of the nature of the disease, a deficiency of the necessary substance might be produced." This existence of intestinal impermeability to the hematopoietic products of gastric activity appears very plausible from the work of Gansslen (1930). He first demonstrated the increased effectiveness of the active principle of liver when given intramuscularly instead of by mouth. This work was later confirmed by Schilling (1931). It therefore appears that the macrocytic anemia produced in certain lesions of the intestinal tract probably is the result of disturbance in either the formation or the absorption of the final effective principle. It recently has been suggested (Eros and Kunos, 1936) that hematopoietic substances are produced not only in the stomach but also in the entire intestinal tract, in other secretory organs, and in all organs containing an argentaffin cell system.

MATERIAL EXAMINED

This paper is based on a series of 20 cases (table 1) in which anemia was associated with lesions of the ileum and colon. These cases have been studied from the standpoint of type of anemia, and the type of lesion has been verified at operation.

TABLE I
Conditions Found at Operation and Type of Anemia Present

Condition found	Number of cases	Macrocytosis or picture of pernicious anemia, cases	Hypochromic, microcytic anemia, cases	Hypochromic, normocytic anemia, cases
Inflammation of terminal portion of ileum	7	6	1	0
Ulcer of the ileum	4	1	1	2
Carcinoma of cecum	3	1	0	2
Fecal fistulas	2	1	1	0
Tuberculosis of ileum and cecum	2	0	2	0
Carcinoma of ileum	1	1	0	0
Diverticulosis of colon and chronic ulcerative colitis	1	1	0	0
Total	20	11	5	4

In seven cases of proved ileitis of the terminal portion of the ileum there were six instances of macrocytic anemia and in the remaining case the anemia was of the microcytic hypochromic type. Apparently, the macrocytosis was not dependent on the degree of involvement of the ileum because

the extent of involvement of the ileum was as great in the case in which microcytosis occurred as it was in the remaining six cases. Hemorrhage was not a factor as it was not present in any of the cases. The patient who had microcytic hypochromic anemia was a male, which would rule out the possibility that a primary microcytic hypochromic anemia might have been the basis for the microcytosis. One of these cases is of particular interest because a diagnosis of pernicious anemia had been made and the patient had received adequate treatment for pernicious anemia before coming to the clinic. Free hydrochloric acid was present in the gastric contents. Large doses of liver extract administered parenterally for 10 days prior to operation did not produce any change in the degree of anemia. There was no increase in the percentage of reticulated erythrocytes. At operation the patient was found to have an extensive inflammation of the lower portion of the ileum with slight obstruction. Following operation the blood picture gradually improved and within one month the number of corpuscles was normal and the erythrocytes were normal in size. During this period no treatment for the anemia was given. In the cases in which the patients survived the operation, the blood rapidly returned to normal without specific treatment. Three patients died following operation.

In the six cases in which macrocytic anemia was present, the erythrocytes were well filled with hemoglobin and closely simulated those found in cases of pernicious anemia. However, there was but little poikilocytosis as compared with the degree usually seen in pernicious anemia. The leukocyte picture as a rule showed a shift of the neutrophils to the left and in no instance was there a shift to the right with thinning and stranding of the individual lobes of the nucleus as is so characteristically seen in cases of pernicious anemia. It thus will be seen that, in spite of a high color index, detailed study of the morphology of the blood will not show the typical features of pernicious anemia and in all such instances detailed study of the patient for a disease other than pernicious anemia should be instigated. It is possible that an individual might have pernicious anemia associated with ileitis. In such instances one would expect the anemia to persist after operation, and there most probably would be symptoms of pernicious anemia, such as glossitis, symptoms of combined sclerosis, and achlorhydria.

Four patients who had an ulcer of the ileum also had hypochromic anemia. In one of these cases the anemia was of the macrocytic hypochromic type, in two cases it was of the normocytic hypochromic type, and in the remaining case it was of the microcytic hypochromic type. In the case in which there was macrocytosis, the ulcer had produced obstruction, whereas in the other three cases there was no obstruction. The patient who had macrocytic hypochromic anemia occasionally had had tarry stools for two months previous to his registration at the clinic. At operation an ulcer was found $11\frac{1}{2}$ feet (45.7 cm) above the ileocecal valve and obstruction was present. Eight centimeters of ileum were removed. The blood returned to normal following operation and the macrocytosis disappeared.

In the other three cases there was no evidence of obstruction and no macrocytosis was found, the erythrocytes were normal in size in two of these cases and microcytic in one case. In one of the cases in which the size of the erythrocytes was normal the patient had had tarry stools for eight years prior to operation. In the case of microcytic hypochromic anemia there was no history of hemorrhage and at operation an inflammatory ulcer was found in a Meckel's diverticulum. The fact that this patient was a male would rule out the possibility of a primary microcytic anemia. In three of these cases the blood returned to normal postoperatively. One of the patients who had hypochromic normocytic anemia died shortly after operation.

In a case of obstructive carcinoma of the terminal portion of the ileum, vomiting was present and there was a macrocytic hypochromic anemia. A normocytic hypochromic anemia was present in three cases of carcinoma of the cecum, in one of these cases there was slight obstruction. The patient who had macrocytic anemia had no symptoms of pernicious anemia, although gastric analysis revealed an absence of free hydrochloric acid. Following operation the macrocytosis disappeared and the blood gradually returned to normal.

In two cases of fecal fistula one of the patients had hypochromic anemia and the other presented the typical blood picture of pernicious anemia although there was less shift of the neutrophils to the right than there usually is in pernicious anemia. The latter patient also had glossitis, numbness and tingling of the fingers and toes, and achlorhydria. Neurologic examination revealed the presence of subacute combined sclerosis and peripheral neuritis. Following operation, the anemia persisted but responded readily to intramuscular administration of liver extract. This patient undoubtedly had a true pernicious anemia with an associated fecal fistula. This patient died a few weeks after operation. The other patient had a hypochromic anemia of the microcytic type. Operation revealed multiple fistulas which involved about 17 cm. of the ileum. The blood returned to normal within three months after operation.

Two patients who had tuberculosis of the terminal portion of the ileum and of the cecum also had a microcytic hypochromic anemia. There was no history of hemorrhage or obstruction in either case. Gastric analysis revealed an absence of free hydrochloric acid in both cases.

One patient who had diverticulosis of the left half of the colon and chronic ulcerative colitis of the right half of the colon also had a macrocytic anemia with high color index. There was no free hydrochloric acid in the gastric contents. The blood did not respond to adequate treatment for pernicious anemia but the patient recovered spontaneously two years after he left the clinic.

COMMENT

It is apparent that regional ileitis may produce a macrocytic anemia which apparently is independent of the amount of involvement of the ileum.

There was as much bowel diseased in one case of microcytic hypochromic anemia as there was in any of the six cases of macrocytic anemia. Hemorrhage was not a factor in this series of cases. There apparently is some abnormality of absorption and a situation possibly is produced in which there is improper utilization of the effective fraction by the liver, for in this group of cases no change in the blood picture was noted after parenteral administration of liver fractions that are effective in the treatment of pernicious anemia. In the two cases of tuberculous involvement of the ileum there was no macrocytic anemia, which may indicate that in such processes there is no abnormality of formation or absorption of the hematopoietic principle. Any lesion of the bowel that produces obstruction may so interfere with the absorption or utilization of the hematopoietic principle that a macrocytic anemia will result. Only one case of diverticulosis of the colon and chronic ulcerative colitis was studied and in this case there was a macrocytic anemia. There was no history of obstruction. The macrocytosis disappeared spontaneously.

TABLE II
Cases of Hypochromic Anemia

Case	Chief complaint	Condition found	Blood picture previous to operation
1	Diarrhea of several months' duration	Extensive inflammation of lower portion of ileum and slight obstruction	Hypochromic, microcytic anemia*
2	Fecal fistula that followed appendectomy two months previously	Multiple fecal fistulas in ileum	Hypochromic, microcytic anemia
3	Intermittent abdominal cramps over entire abdomen for 10 years	Tuberculosis of terminal two feet of ileum and of cecum, with slight obstruction	Hypochromic, microcytic anemia
4	Intermittent cramps in left upper quadrant of abdomen for two years	Tuberculosis of terminal two feet of ileum and of cecum	Hypochromic, microcytic anemia
5	Intermittent cramping pains across midabdomen for 18 months	Simple solitary ulcer of ileum, 2 cm in diameter	Hypochromic, normocytic anemia*
6	Tarry and bloody stools intermittently for eight years	Inflammatory annular ulcer of ileum, involving 10 cm of ileum	Hypochromic, normocytic anemia
7	Intermittent abdominal cramping pains for three years	Angulated loop of ileum with Meckel's diverticulum which contained an inflammatory ulcer	Hypochromic, microcytic anemia
8	Intermittent cramping pains in left lower quadrant of abdomen for two months	Perforating carcinoma of cecum with involvement of 10 cm of ileum	Hypochromic, normocytic anemia
9	Colicky pains in right lower quadrant of abdomen and diarrhea of six months' duration	Cecal carcinoma (grade 2) with partial obstruction of lower portion of ileum	Hypochromic, normocytic anemia

* Patient died following operation

If macrocytic anemia is attributable only to failure of absorption of the effective hematopoietic principle, the anemia should respond to effective liver fractions administered parenterally, but this did not occur in two cases in which the patients were adequately treated. It would appear that in regional ileitis particularly, the process in some manner produces some change, perhaps in the form of a toxin, which prevents utilization of the hematopoietic principle by the liver. Since in most instances, as has been previously stated,

TABLE III
Cases with Blood Picture of Pernicious Anemia or Macrocytosis

Case	Chief complaint	Condition found	Blood picture previous to operation
1	Intermittent cramping abdominal pains for eight years	Inflammation of terminal portion of ileum and dilated loops of intestine	Macrocytosis
2	Dull, intermittent abdominal cramps for three years	Distal 25 to 30 cm of ileum involved in inflammatory reaction	Macrocytosis*
3	Constipation for 20 years	Regional ileitis	Macrocytosis*
4	Intermittent low cramping abdominal pain for five years	Inflammation of terminal portion of ileum, with some dilatation and obstruction	Macrocytic, hypochromic anemia
5	Numbness and tingling of hands and feet, pain in right lower quadrant of abdomen, diarrhea for three months	Inflammatory lesion involving cecum and 8 cm of ileum	Macrocytic, hypochromic anemia
6	Cramping, intermittent pains in right lower quadrant of abdomen for two years. Condition diagnosed as pernicious anemia and patient treated with liver before admission	Extensive inflammation of lower portion of ileum with slight obstruction	Pernicious anemia
7	Cramping pain in right lower abdominal quadrant with vomiting for two months	Carcinoma of terminal portion of ileum with obstruction	Macrocytosis
8	Recurrent numbness and tingling of the feet and hands for nine years, constant dull aching pain in right upper quadrant of abdomen for one month	Diverticulosis of the left half of colon and chronic ulcerative colitis of the right half of colon	Macrocytosis
9	Anemia and weakness for one year	Carcinoma (grade 2) of cecum	Slight macrocytosis suggestive of pernicious anemia
10	Intermittent abdominal cramps for four years and severe cramping pain in lower part of abdomen for seven months	Subacute ulcer of ileum with partial obstruction	Macrocytosis
11	Numbness and tingling of hands and feet with sore tongue for eight weeks, fecal fistula for 12 years, diarrhea for one year	Multiple fecal fistula of the small intestine	Pernicious anemia*

* Patient died following operation

the blood picture can be distinguished from that seen in pernicious anemia, the finding suggests that factors other than failure of absorption and utilization of the hematopoietic principle may produce a macrocytic type of anemia

Since the macrocytosis and anemia disappeared following operation in this series of cases, it would not seem essential to treat such an anemia with materials effective in the treatment of pernicious anemia. It seems to us, however, that for good therapeutics such preparations should be used and preferably by the parenteral method as this should result in a rapid response of the blood to normal. One should have constantly in mind the possible coexistence of pernicious anemia, and in cases in which the clinical findings support a diagnosis of pernicious anemia, the treatment must be continued after operative procedures.

The most outstanding symptom in this series of cases was cramping abdominal pain (tables 2 and 3). We wish to emphasize that this symptom, particularly in the presence of macrocytic anemia without symptoms of pernicious anemia, strongly suggests a lesion of the ileum.

It also should be emphasized that macrocytic anemia does not always mean pernicious anemia or sprue, but in such cases patients should be studied in detail to eliminate lesions of the small intestine or liver. This is especially true if the patient presents none of the symptoms of pernicious anemia.

SUMMARY

Macrocytic anemia frequently affects individuals who are suffering from regional ileitis. Any intestinal lesion which produces obstruction may produce a macrocytic anemia. Carcinoma of the cecum, tuberculous ileitis, and fecal fistulas did not produce a macrocytic anemia.

Parenteral administration of liver was not effective in the treatment of the anemia associated with regional ileitis. The condition of the blood improved spontaneously following operation. Coexistence of pernicious anemia and lesions of the intestine has been considered.

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MEDICO-DENTAL RELATIONS, THE DENTIST'S VIEWPOINT *

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THE question of medico-dental relations is one which has been discussed for many years. It was originally prompted by the empirical findings of those early practitioners who had observed either a favorable response to the elimination of certain oral conditions, or the damaging effects of faulty dental technology. The case reports of Benjamin Rush and his contemporaries on the benefits frequently accompanying the elimination of oral infections are well known. The period in which these early practitioners lived did not offer such opportunities for investigation as exist today, yet their frequent reports on medico-dental relations are not without value.

The first school of dentistry was founded (1840) with full recognition of the existence and value of the then known medico-dental relations. The objectives of the school according to one of its founders, Chapin A. Harris, M D,¹ is "to give those who receive its instructions a thorough medico-dental education, so that when they enter upon the active duties of the profession they may be enabled to practice it, not alone as a mere mechanical art, but upon sound scientific principles, as a regular branch of medicine." Dr. Thomas Bond, one of the faculty of the first school, states in the introduction to his *Practical Treatise on Dental Medicine*² that "the purpose of the present work is to present to the reader a digest of information prepared with particular reference to the morbid connections certainly existing between the teeth and the rest of the body."

The handicaps imposed by the continued existence of apprenticeship methods, the rise of commercialism in many dental schools, inhibited the attainment of the health service objectives of the early schools, and dentistry for the most part continued to limit its activities to dental technology. Medicine, busy creating and utilizing new knowledge in its field, also left untouched areas now recognized as having medico-dental relations. It was not until the early part of the twentieth century that the findings of Hunter, Billings and others stimulated interest and further investigation into the possible relations which oral infections may have as etiologic factors in systemic disease. Though early interest and enthusiasm on the subject were accompanied by many misinterpretations which have led to radical and fanatic therapy, that period fortunately is about ended, and an era characterized by conservative, though progressive, attitudes has now begun.

The modern concept of medico-dental relations includes, in so far as

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we have been able to determine, several general phases namely, the effects which oral diseases or disorders may have as etiologic factors in systemic disease, in the aggravation of already existing conditions, in the establishment of a negative phase of body defense factors, as the cause of certain reflex disturbances, and finally, the changes in the oral hard and soft tissues due to systemic disease or metabolic disorder. Obviously there is in each phase the same difficulty in establishing absolute proof that exists in connection with the etiology of many diseases.

McNevin and Vaughan,⁴ in a discussion of focal infection, state that (1) "Even if absolute proof of the existence of oral and other foci of infection cannot be submitted, it is nevertheless a reasonable assumption", that (2) "The strong circumstantial evidence advanced, strengthens the assumption", and (3) "The exact nature, however, of the effect which oral foci exert on the body, in each case cannot always be determined". From the viewpoint of the dentist, it is not any spectacular nature or effect of oral foci which should cause them to command attention, but rather the great frequency with which they occur. It is one thing to attach little importance to a single oral lesion, but quite another to disregard the probable effects of many carious teeth, or multiple supporting tissue lesions, in the mouth of one patient. It is the rare individual today who does not harbor either one important or several minor foci. Clinical search for spectacular or potent oral foci often overshadows consideration of the long range effects of those of apparently lesser and more immediate import. If it be true that most diseases are due to a combination of forces, may it not be said that apparently harmless multiple foci constitute a force, which though it may not be the most active, is nevertheless a needless burden to the individual? Perhaps we dwell too heavily on this point, however, it is prompted by the appallingly high incidence of mouth filth, dental caries, and so-called pyorrhea among American people. One has but to examine several thousand adults or children to reach the conclusion that a large number are carrying multiple oral foci which should be eliminated.

Much has been written regarding the routes by which the products of oral sepsis may be transported to other parts. For the most part, emphasis on the spread of infection by the blood and lymph stream has excluded consideration of the probable effects of transfer by swallowing, aspiration, or by continuity of tissue. Because of the location of oral infections and the great frequency with which they occur, should not these avenues for the spread of septic products be rated higher in importance than they now are? Even though the transfer of infection by continuity of tissue, aspiration or swallowing be regarded as devoid of significance in the etiology of respiratory or gastrointestinal diseases, may it not impose aggravating factors which make successful treatment difficult? In view of the widespread lack of mouth hygiene, the high incidence of dental caries and pyorrhea, it is not illogical to assume that effective mouth hygiene offers some protection against certain respiratory or gastrointestinal diseases.

The physician should have knowledge of all of the oral disease or disorders of his patient, therefore, the report of the dentist should be a comprehensive one, going far beyond the now too common, and too limited statement as to the patient's oral condition. These reports, I believe, should include data relative to conditions which may bear causal relations to systemic disease. There are good reasons for the assumption that there should be included information as to the extent of dental caries, pulpless teeth, infections of the periodontal tissues, alveolar abscesses, residual infection, impacted teeth, mouth filth, and marked malocclusion.

Dental caries, the most frequently occurring physical defect among civilized peoples, has for years been regarded as a condition to be treated from a point of tooth conservation. From research findings and clinical observation one is led to conclude that dental caries, especially in youth, may be regarded as an important focus of infection. It has been shown by Noyes, Fish and others that fluids may easily be passed through the tubules of the dentin to the pulp. Hartzell and Henrici⁴ state that, "Our results confirm in a general way the studies of Collins and Lyne. If our observations are correct we must conclude that in approximately one-half of the number of teeth invaded by caries or surrounded by pyorrhea, the pulps are already infected by streptococci." In 1920 these investigators state that subsequent studies give "ample confirmation of the opinion previously arrived at from bacteriological studies that the pulp may be (a) invaded by microorganisms long before it is actually exposed by caries, and (b) may be repeatedly injured by microorganisms long before it actually undergoes necrosis." Thoma⁵ has shown that the *Streptococcus viridans* is the most important factor in pulp infection. He states that in 16 out of 21 cases with closed pulp chambers pure cultures of *Streptococcus viridans* were produced, and concludes that "an infected vital pulp, no matter whether there are marked periapical changes or not, is often a very important focus of infection."

The evidences of favorable response to the treatment of dental caries is too frequent to put to one side as being without significance. The elimination of lymphadenitis, and the increase in alertness and in general well-being have been observed many times in this country and abroad. While there are involved such other factors as the relief of pain and more effective mastication, we believe that treatment which stops the transfer of septic products through the tubules of the dentin to the pulp under biting stress or perhaps without it, is in the main responsible.

The oral focus about which more has been written than any other is the chronic alveolar infection. Presenting as it does a closed focus, there is much to prove that it is a common etiologic factor in diseases of adjacent and remote structures. It would be out of place here to enumerate the list of specific conditions commonly ascribed to these foci. It should be said, however, that it is all too common practice to consider chronic alveolar abscesses as the only oral source of focal infection. There is no sound basis for the apparent exclusion of other foci which may also be present. Neither

are there any grounds for the optimism so frequently encountered in the absence of gross radiographic evidence. Any estimate of the effects of these infections as judged by radiographic evidence is obviously unreliable. It has not yet been shown that pulpless teeth can be successfully treated, and until this proof is at hand, protection of the patient should warrant their removal. Statements that the extraction of such teeth is not always followed by a favorable response are somewhat beyond the point. Dental infections may not have been a cause of the disease under consideration, however, they should be rated as potentially dangerous and therefore eliminated.

As to the condition commonly called pyorrhea, there appears to be much confusion as to the part which it may play in systemic infection. Much of the confusion results from the fact that all too frequently all changes in the supporting tissues of the teeth are included under the term pyorrhea. Atrophic changes, so-called recession, of the alveolar and periodontal tissues are unimportant as etiologic factors in focal infection, however, because these atrophic changes are often accompanied by increased mobility of the teeth, a focus of infection is often assumed to exist and extraction of the teeth is advised. It is the periodontal infection, or the suppurating pyorrhea pocket, which should command the interest of the physician. The tissues involved in this condition, abundantly supplied as they are with lymphatic and capillary blood vessels, offer many avenues for the extension of bacteria and their products. The disease should be regarded as a focus of infection of considerable importance, not only because it affords opportunities for metastasis, but also for the reason that drainage from the suppurating tissues tends to raise the oral bacterial count to a high point. The accompanying increase in mouth bacteria, though usually disregarded, may in chronic suppurating infection of the alveoli and periodontal tissues establish by a spread of infection through aspiration, continuity of tissue, or swallowing, relations to diseases of the gastrointestinal, and upper and lower respiratory tract. Whether or not one accepts mouth bacteria as bearing causal relations to these diseases, it appears that in their treatment at least, the establishment and maintenance of mouth hygiene should be good routine practice.

Yet another common oral source of infection is seen in the residual areas remaining in the soft tissue of alveolar bone following the removal of teeth. They are caused by leaving infected root apices, cysts, foreign bodies, loose particles of alveolar bone, or by the incomplete removal of pathologic tissue. These residual areas are so frequently found in the partially or completely edentulous jaw, that the absence of teeth still leaves ground for suspicion that such areas may exist. It is also good routine practice to suspect the presence of unerupted teeth in the edentulous jaw. The patient is not usually conscious of the presence of residual areas, unless symptoms of acute infection arise, therefore, for practical diagnostic purposes absence of local symptoms does not warrant the assumption that these areas do not exist and bear some relation to diseases of adjacent or remote tissues.

In addition to oral infections and their possible relations to systemic disease, the reflex disturbance frequently established by unerupted and impacted teeth, pulp stones and sclerotic bone are of interest. The removal of these occasional causes of reflex disturbance have so often brought relief, that they should be of considerable import in oral diagnosis.

In considering oral infections in their relation to systemic disease, it is frequently stated that individuals may carry most of them without apparent harm. However, one must conclude that the body defense factors are not inexhaustible, and even though one held that oral infections are devoid of direct causal relations in systemic disease, it would be difficult to justify a premise which held that they did not constitute a needless burden which tended to jeopardize the defensive powers of the individual. In persons who have lost much of their normal defense, the coexistence of chronic oral infections with systemic disease is too frequent to be overlooked.

It is interesting to note the views of Haden,⁶ who states that "In studying patients with systemic disease of focal origin, all possible foci of infection should have careful clinical consideration. Every student of focal infection is impressed with the fact that no subject in medicine must be handled with more mature clinical judgment when one sees the harmful results of the reckless removal of teeth, the frequent ascribing of conditions to focal infection when due to entirely different causes, and careless promises for the relief of systemic lesions by the extraction of teeth. Careful study of the subject must convince one of the importance of dental focal infection in the causation of systemic disease."

Pemberton,⁷ in speaking of the removal of focal infection in arthritis, makes an excellent point when he states that "Much emphasis will be placed here upon the removal of focal infection, but the importance of a medical understanding of the individual as a whole precedes this. Notwithstanding the theoretical propriety of removing infections, any step in this direction may, especially in the later stages, be not only unprofitable but dangerous." This statement is especially applicable to the removal of oral infections. Very frequently when systemic disease demands the removal of these infections, the extraction of a number of teeth at one period is followed by severe reactions and exacerbation of the patient's symptoms. In the terminal diseases, the gradual elimination of oral infections, sometimes over a period of weeks appears to be good practice.

Another side of the question of medico-dental relations includes those points at which the dentist should refer his patient to the physician. In general this is indicated when (a) it is thought that systemic conditions are etiologic factors in the establishment and maintenance of certain oral diseases, disorders or deficiencies, and (b) when oral manifestations of systemic disease, for which the patient is not being treated, are recognized by the dentist. To the end that graduates in dentistry shall be more capable of initiating intelligent action on these two points, American dental education has made important changes in its curriculum and objectives.

As yet the exciting cause of dental caries is unknown, therefore preventive measures are for the most part empirical. There appears, however, to be general recognition of the value of high structural resistance to dental caries, and to the protection afforded by harmonious and adequate development of jaws and teeth. Inasmuch as tooth development begins in intra-uterine life, and as the follicles of both the deciduous and permanent teeth are developed at birth, one may well say that the problem of satisfactory development, and the prevention of dental caries in part at least, up to the eruption of the first tooth, is one for the physician. It is well known that up to this point many things may happen to prevent harmonious development. Over these disturbing factors, the dentist has no control. Therefore, the physician must in the main be responsible for the inauguration of such preventive or therapeutic measures as may be necessary.

It is difficult to agree with those who approach the problem of arresting or preventing dental caries through dietary measures alone. The simple administration of calcium or phosphorus compounds and vitamin bearing substances guarantees little, unless it can be shown that dietary deficiencies actually exist. Medical understanding of the patient as a whole is necessary for the reason that many factors may prohibit assimilation and fixation of inorganic salts. The patient may be suffering from some systemic disease or metabolic disorder or may be eliminating desirable inorganic salts too rapidly. Diagnosis by the physician should be the basis for judgment in the matter of diet as a preventive measure in dental caries. The physician and the dentist, cooperating in arresting or preventing this widespread condition, can accomplish much more than can either one alone.

The frequent need for cooperation of the internist is evident in the prevention and treatment of supporting changes (pyorrhea) when one considers the constitutional factors usually involved. These changes seldom occur before middle age, and are rarely established in a marked way so long as the patient has sufficient resistance to withstand the burdens imposed by such local factors as malocclusion, faulty restorative work, or inadequate mouth hygiene. Obviously certain changes can be accounted for in terms of advancing age, however, both acute and chronic systemic disorders usually leave their mark on the alveolar and periodontal tissues and in addition lower their resistance to infectious and mechanical stresses. These oral manifestations of metabolic disturbances present a much wider field than is ordinarily thought. They include such conditions as diabetes which, in addition to lowering resistance, may be accompanied by changes in the oral mucous membrane, anemias, with their frequent oral symptoms, malnutrition with its accompanying deficiencies, nephritis and many other conditions which obviously need not be considered here. It is sufficient to repeat that such conditions play no small part in disturbing the health of the alveolar and periodontal tissues. Most human dentures are so poorly developed, or become so damaged through caries, that harmonious function of the denture is impossible. Factors of ill health imposed on existing disharmonies often

bring about complete edentulation in early middle life. The search for a single local etiologic factor in supporting tissue changes, or the attempt to prevent or successfully treat these conditions as purely local changes, is for the most part futile. Diagnosis and treatment by the internist in a large number of cases is either a prerequisite to or accompaniment of successful dental service in preventing or treating these conditions.

The illustrations which have been drawn serve only to show examples of areas having medico-dental relations. In the past these areas have been relatively untouched by either medicine or dentistry. Dentistry largely because of certain heritages which it had difficulty in overcoming, centered its efforts for the most part on restorative and replacement procedures. As research and clinical observation caused revival of interest in the relation of oral sepsis to systemic disease, changes in attitude began to take place. The key to the solution of the problem, dental education, was stimulated by an excellent report on dental education by the Carnegie Foundation. Among other things this report held that dentistry "properly a form of health service," expanded as it should be in biological scope and strengthened in its health service aspects, would be devoted, "to detection and provisional diagnosis of dental and oral symptoms that indicate the prevalence or imply the probable existence of ill health elsewhere in the body and to suitable, supplemental, advisory health service including consultation with the patient's physician, based on such observation and diagnosis."

Following a four year curriculum study in which medico-dental relations played an important part, the American Association of Dental Schools adopted among other objectives of dental education, those which call for the education of students in order that they may be (*a*) competent in the maintenance of oral health, and in the treatment of oral diseases, disorders and deficiencies with understanding and appreciation of the relationships between oral and systemic conditions in health and disease, and (*b*) be able to cooperate effectively with persons engaged in allied fields of service. Recommendations relative to a suggested curriculum leading to attainment of these objectives were also adopted by the Association.

There is sound basis for anticipating that research and clinical observations will show even more important and more extensive medico-dental relations than are now thought to exist. Utilization of knowledge in the areas which have so long been neglected depends primarily on education and cooperation. Dental education is taking many forward steps and by 1937 nearly all dental schools will require two years' pre-dental work for admission to improved four year courses. Dental organizations are becoming increasingly more active in the promotion of research in the biological phases of dentistry. In general, trends indicate a healthy forward movement to new goals and to the acceptance of broader responsibilities in the health service field.

In closing, may I express appreciation for the cooperative spirit with which medicine has approached problems involving medico-dental relation-

ships It has been both helpful and encouraging Continued and extended cooperation between the two professions will, I am certain, mean much to the patient, the physician, and the dentist

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CASE REPORTS

ACUTE GUMMATOUS MYOCARDITIS SIMULATING ACUTE MYOCARDIAL INFARCTION¹

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CORONARY thrombosis was rarely diagnosed ante mortem prior to 1918. At that time textbooks on medicine contained no reference to the clinical condition. It is a tribute to American medicine that the clinical recognition of cardiac infarction is due to the observations and studies of American physicians.

Osler¹ was familiar with the condition. Dock² was one of the first to describe a case which had been diagnosed ante mortem. However, its significance was not appreciated until Herrick in 1912³ and again in 1918⁴ had described its clinical features and drawn attention to the fact that it could be easily diagnosed and that many cases recovered.

The importance of the subject soon became quite apparent, so that within a comparatively short time it was more frequently recognized and diagnosed, at first, as is usual, in places where teaching was done. The transition in the state of our knowledge of the condition was ably expressed by Christian⁵ in 1925: "Twenty-five years ago, cardiac infarction as a result of coronary thrombosis had been shown to me in the postmortem room but I recall no reference to cardiac infarction or, as it is sometimes termed, coronary thrombosis, as a condition to be recognized during life. My teachers of that day seemed unable to make the diagnosis in the clinic. Today I find that fourth year medical students in my wards at the Peter Bent Brigham Hospital consider it in rendering a diagnosis on a patient assigned to them for history and physical examination, and adopt or eliminate it with a very considerable degree of accuracy. In other words, the students of today diagnose with much accuracy a condition that was hardly known to medical students twenty-five years ago."

The older practicing physicians were naturally slower to appreciate the condition. However, with increasing knowledge, they too have become familiar with it, so that today coronary thrombosis is frequently and usually correctly diagnosed by the practicing physician. Hamman⁶ expresses very well the change which has occurred: "Ten years ago I was often called to see patients with symptoms of collapse following a severe attack of pain in the chest, and under these circumstances had the satisfaction of pointing out how simply the diagnosis of coronary thrombosis could be made. Today the humblest practitioner of medicine is so familiar with the clinical picture and so alive to its recognition that the opinion of the consultant is seldom needed to suggest the diagnosis. Now when almost every sudden pain in the chest of a person past middle life is called coronary occlusion, it seems appropriate to sound a warning. There are other diseases of the heart, lungs, and abdominal organs which so closely

¹ Read at the Detroit meeting of the American College of Physicians, March 6, 1936.
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resemble coronary occlusion that they are often distinguishable from it only with great difficulty and sometimes not until autopsy discloses in detail the real state of affairs."

This coincides with my experience. Paradoxically, the consultant no longer introduces the diagnosis of myocardial infarction, but now either confirms it or diagnoses one of the less common but equally important conditions simulating myocardial infarction.

Naturally, at first mistakes in diagnosis occurred because the clinical condition was not clearly understood. One of the errors was to diagnose an acute surgical condition in the abdomen because of the prominence of the abdominal symptoms, and in several instances exploration of the abdomen was done and no pathology found. Later the correct diagnosis was shown at autopsy. Levine and Tranter⁷ and later others, Hamburger,⁸ Hardt,⁹ Anderson,¹⁰ Coffen and Rush,¹¹ Portis,¹² directed attention to this phase of the problem.

Now the situation is reversed. Failure to recognize myocardial infarction rarely occurs. In fact, it is sometimes erroneously diagnosed in the presence of conditions which resemble it. The error may prove serious or even fatal to the patient, especially if the condition is one which could have been relieved by proper medical or surgical procedures. Within the past few years the literature on this subject has contained reports of various conditions which simulate myocardial infarction. Among these are acute pericarditis,^{6, 20} pulmonary embolism,^{1, 15, 16, 17, 20} acute upper abdominal disease,^{6, 8, 19, 20, 21, 20} interstitial emphysema,⁶ ruptured aorta,^{6, 26, 27} dissecting aneurysm of the aorta,^{22, 23} ruptured aortic,²⁸ spontaneous pneumothorax,²⁹ sudden change in the rhythm of the heart.^{30, 31}

I have seen examples of many of these and I have also seen in consultation and on the wards of the University Hospital instances where coronary thrombosis was diagnosed, and the condition later shown to be acute mediastinitis, severe hemorrhage from a duodenal ulcer, acute acidosis associated with diabetes.

It is the purpose of this communication to draw attention to still another condition which presents a confusing resemblance to coronary thrombosis. A patient was observed on the wards of the University Hospital with the symptoms, physical signs, blood pressure readings, laboratory findings, electrocardiographic evidence and clinical course usually considered characteristic of acute myocardial infarction. This similarity justifies the presentation of the details of the case.

CASE REPORT

A white male truck driver, aged 26 years, was admitted to the University Hospital July 6, 1932, acutely ill, complaining of constriction beneath the lower end of the sternum and the upper abdomen and nausea and vomiting of three days' duration. His family history was unimportant. The patient had been married seven years, his wife and one child five years of age were living. Three years ago his wife had a miscarriage at the third month of pregnancy the cause of which was undetermined. Prior to the past year he was employed as a truck driver for a lumber and trucking company and since that time he had done odd jobs as a laborer. During childhood he had measles, mumps, pertussis and scarlet fever. There was no history of diphtheria, pneumonia or rheumatic fever. Seven years before admission he had had a chancre and a gonorrheal infection, two years later he had a generalized body eruption which had reappeared three months prior to admission. Because of the recurrence of the

rash and a four plus Wassermann reaction, he was given a series of intravenous and intramuscular injections. This therapy was discontinued two weeks before admission because of the appearance of a dry, scaly dermatitis upon the hands and the face. His wife, who had also been receiving treatments for syphilis, was then a patient in the University Hospital dangerously ill with a severe form of dermatitis exfoliativa resulting from arsenical medication.

The present illness began on July 3, 1932, three days before admission, with pain and constriction in the lower chest and upper abdomen, nausea, and vomiting. The symptoms persisted and were associated with a non-productive cough, generalized soreness throughout the body, extreme weakness and exhaustion, and severe pain in the lower lumbar region that was aggravated by motion.

The physical examination showed the patient to be acutely ill, in shock, dyspneic, complaining bitterly of a sense of constriction in his chest. The skin revealed a rash with scaly, psoriasis-like lesions located on the abdomen, the arms, and the legs, and also many macules and papules, particularly prominent on the palms of the hands and the soles of the feet. The tongue was red and dry. The oral hygiene was poor and the teeth were decayed. There was no general adenopathy. The veins of the neck were not prominent. The examination of the lungs failed to reveal abnormal findings. The apex beat of the heart could be neither seen nor felt, no cardiac enlargement could be found, and the heart sounds were of faint intensity. The apex rate was 100 beats per minute with regular rhythm. The radial pulse was very feeble and could scarcely be detected. The blood pressure reading was 106 systolic and 80 diastolic. The superficial and deep reflexes were absent. The edges of the spleen and liver were not palpated. There was no pitting edema of the extremities. The temperature on admission was 98 degrees. The following day the temperature was found to be 102.8°, pulse 100, respiration 20. The blood count was as follows: Hemoglobin 89 per cent, red blood cells 5,200,000, white blood cells 23,300, polymorphonuclears 87 per cent, lymphocytes 13 per cent. The examination of the urine showed two plus albumin with numerous hyalin and granular casts. There was an elevated non-protein nitrogen (66.6 milligrams per cent) and a blood sugar of 129 milligrams per cent. The electrocardiogram showed a high take-off of the T-wave in Lead I, with an abnormal take-off of the T-wave in Lead III, having the pattern usually seen in acute myocardial infarction. At this time the heart sounds were less intense, gallop rhythm was present, and moisture appeared in the lungs posteriorly.

The dermatological service reported: "This patient shows a condition suggesting psoriasis by the color, distribution and grouping of the lesions on the abdomen, chest and legs, however, it may possibly be a papulo-squamous syphilitic or arsenical dermatitis."

During the 14 days that he was in the hospital, he continued to have an elevated temperature (figure 1), an increased pulse rate and a persistent leukocytosis. The sedimentation time of the blood was 1 hour and 12 minutes, the blood non-protein nitrogen level varied from 66.6 milligrams per cent to 198 milligrams per cent. The blood Wassermann on admission was reported as showing partial fixation with both antigens, while the second Wassermann reaction was reported as negative. The Wassermann reaction on the spinal fluid was also negative. Electrocardiograms were made every two days and showed consecutive changes (figure 2). The heart sounds continued to vary in intensity with definite gallop rhythm. The blood pressure gradually dropped to 90 systolic and 60 diastolic, signs of circulatory failure increased, and 14 days after admission he expired.

A partial autopsy was performed at the University Hospital July 20, 1932, by Dr. R. B. Hartsfield of the Department of Pathology. "The examination of the peritoneal cavity was negative with the exception of the enlargement of the mesenteric

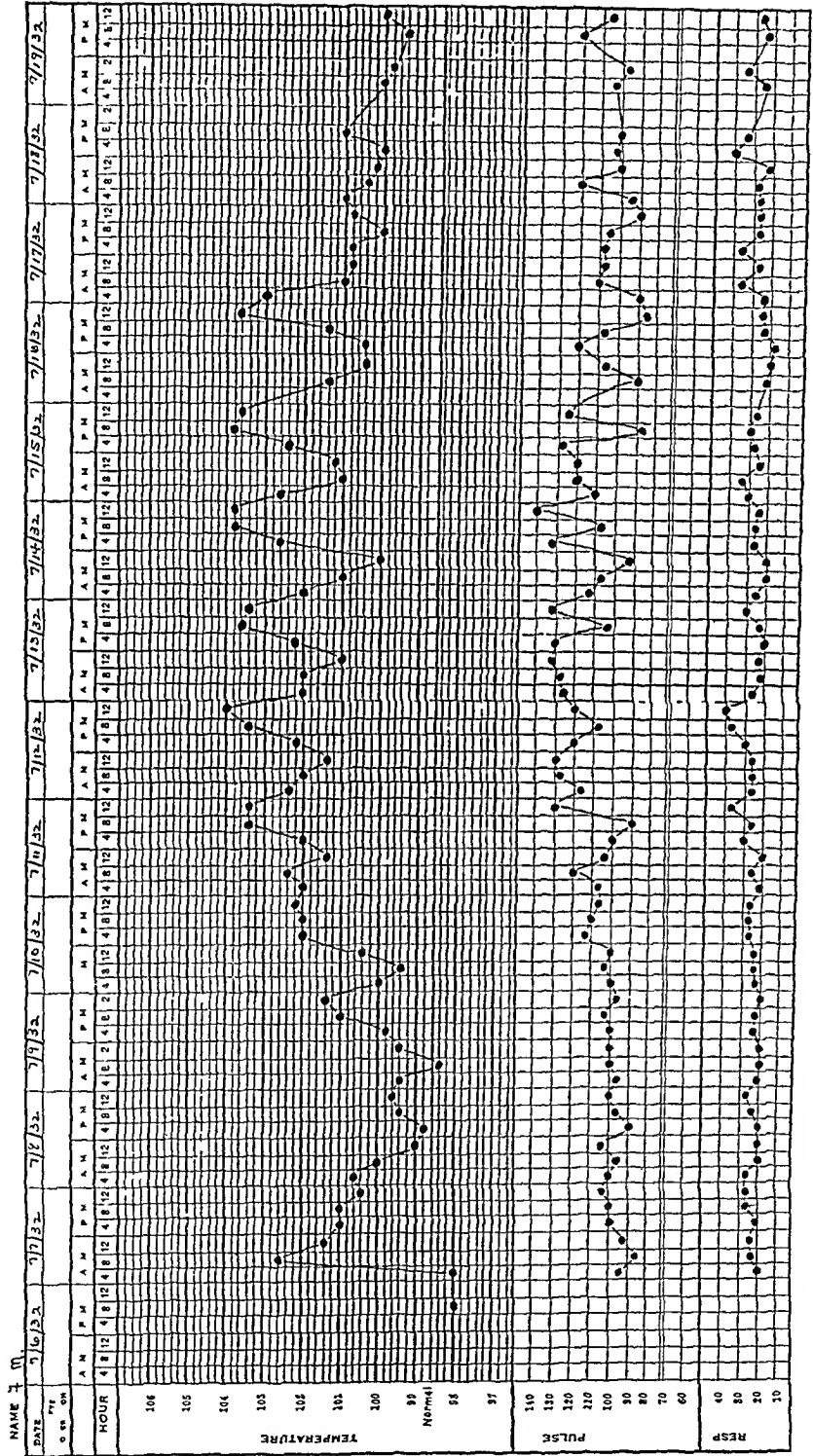


Fig 1

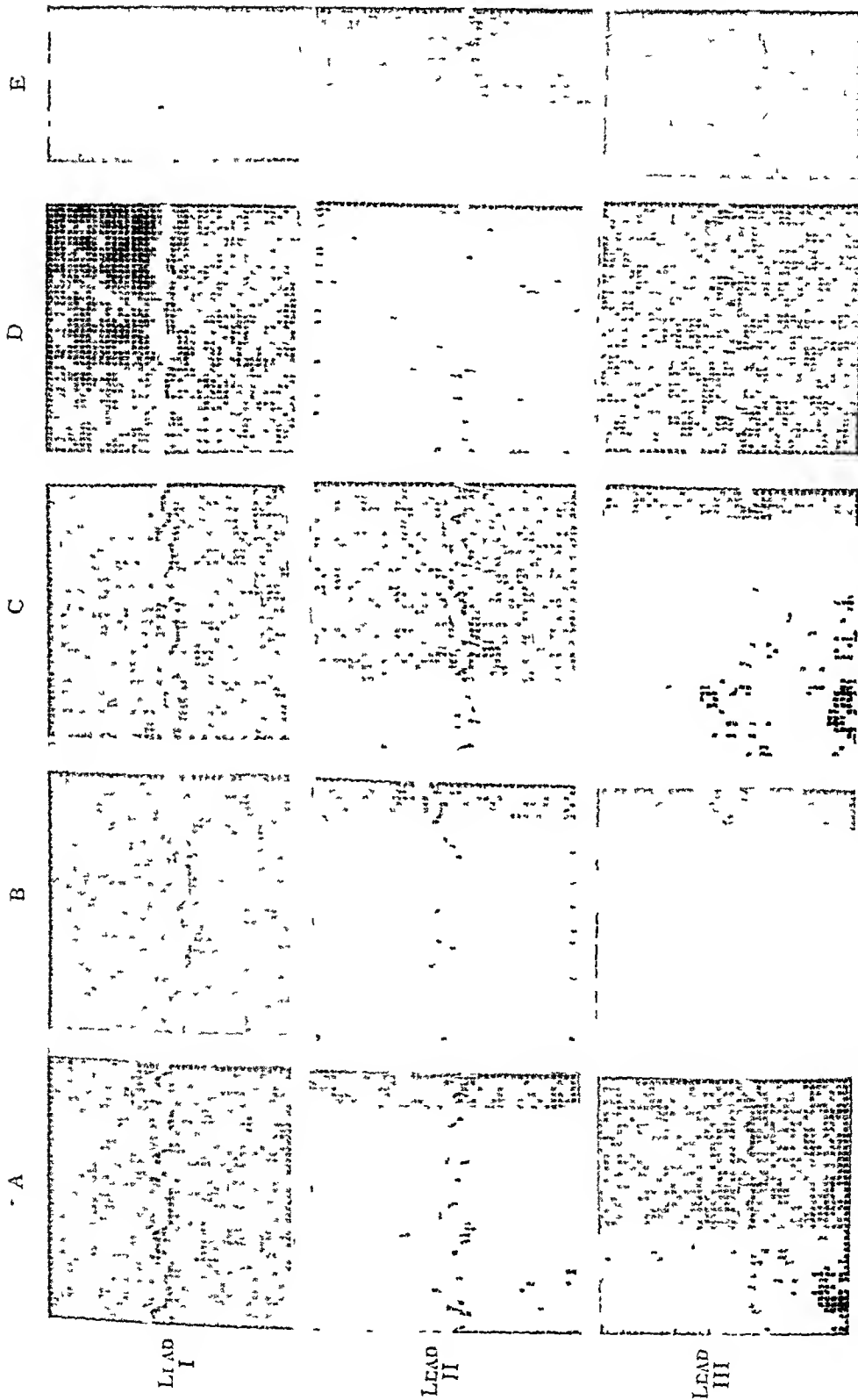


FIG 2 A—Electrocardiogram taken four days after onset B, C, D, E—Taken at two day intervals Note successive changes in the R-S-T complexes in Leads I and III

lymph nodes Both pleural cavities contained 100 c.c. of slightly blood tinged fluid The pericardial cavity was without evident lesion The heart was found to be somewhat larger than usual and on the exterior surface showed a few milk patches The aortic valve showed some thickening along the line of closure The area of the aorta attached to the heart was considerably thickened and showed pearly gray elevations The other vessels showed nothing unusual The endocardium was somewhat lighter in color than usual The myocardium was lighter in color than usual and there were areas scattered throughout having a reddish streaked appearance This was notably marked in the left ventricle The coronary arteries showed a moderate amount of yellowish thickening, however, no areas of occlusion and no thrombus were found The external surface of the lungs was reddish in color and scattered over the surface of both lungs there were found slightly elevated reddish areas ranging from 1 cm to 3 cm in diameter On section these areas extended down into the lungs and were fairly well demarcated, considerably reddish in color and firmer than the surrounding tissue The remainder of the lung tissue was crepitant throughout The spleen was without evident lesion The liver margins were somewhat rounded, on section the cut surface was mottled yellowish and brownish in color The kidneys showed nothing unusual on external examination On section one small area on the right and two small areas on the left were found that were gray in color and slightly demarcated with a slightly hemorrhagic edge The remainder of the kidney section was not remarkable The capsules stripped with slight difficulty leaving a smooth surface The aorta showed marked thickening and some calcification of the thoracic portion The area above the celiac axis showed similar thickening Mingled with the yellowish elevations were pearly gray elevations which appeared to be the pre-

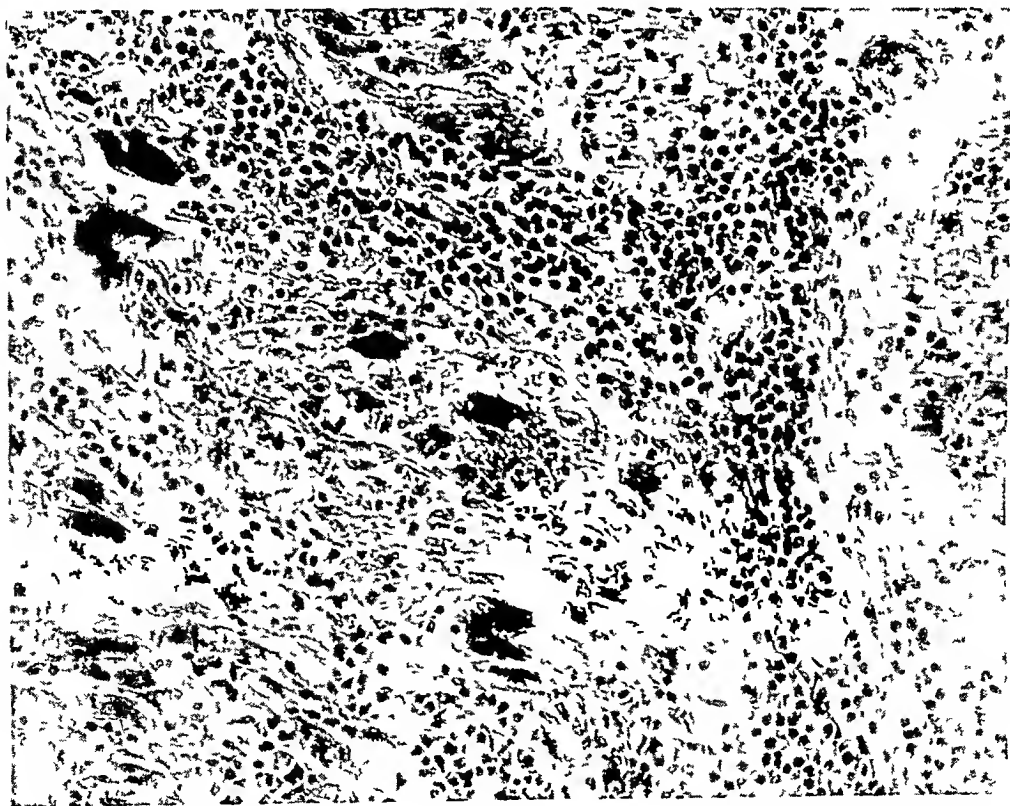


FIG 3 Heart muscle Area of necrosis showing giant cells in mononuclear reaction

dominating lesion. There was considerable longitudinal wrinkling of the intima. This was most marked in the arch of the aorta which appeared to be slightly dilated. The anatomical diagnosis was syphilitic aortitis, apparent acute myocarditis, multiple infarction of the kidney, multiple infarction of the lungs. "The microscopic examination of the aorta revealed lesions typical of syphilitic aortitis. Examination of the heart muscle showed giant cells in areas showing mononuclear reaction (figure 3). The examination of the aorta and the heart muscle for spirochetes was negative."

DISCUSSION

The symptoms, physical signs, leukocytosis, elevated temperature, increased sedimentation time, and repeated abnormal electrocardiograms warranted a diagnosis of myocardial infarction due to coronary thrombosis, but in an attempt to associate this condition with syphilis, one encountered certain difficulties. It is generally agreed by most writers that syphilis is rarely the cause of coronary thrombosis. Levine³² stated that 4.5 per cent of his cases of coronary thrombosis were syphilitic and that it would not follow that even in these syphilis had a direct causative influence in the coronary thrombosis. That it was so of the patient, aged 36, who was the youngest of his series, seemed likely.

Syphilis is supposed to affect the myocardium in the following ways: (1) Specific fibrous myocarditis of Warthin, (2) Gummatous myocarditis, (3) Involvement of the coronaries either at the ostium or by producing an endarteritis. In our patient, although it was evident that the myocardium was damaged, syphilitic myocarditis did not seem to be the logical diagnosis because the existence of the specific fibrous form has not been definitely proved and because of the rarity of the gummatous type. Pathological studies by Scott,³³ Clawson and Bell,³⁴ Maitland,³⁵ and Saphir³⁶ would indicate that there is no specific form of myocarditis due to syphilis, notwithstanding the observations made by Warthin.³⁷ The pathologist has been unable to differentiate the fibrous changes found in the myocardium in known syphilis from the fibrous changes found in other conditions including arteriosclerosis. This fact and the failure to find spirochetes in the myocardium have been used as evidence against Warthin's³⁷ concept that a specific form of myocarditis is found in syphilis. MacCallum³⁸ states that it is fairly self evident that syphilitic disease of the myocardium could occur in the form described by Warthin, and that it could heal with the traces indicated by such scars is equally clear, but he has seen very few cases in which active syphilitic myocarditis was suggested and has been unable to feel sure that the scars found in the myocardium were really syphilitic. Warthin's views have been supported in some instances by Boyd,³⁹ Wilson,⁴⁰ Paulin,⁴¹ and Hamman and Rich.⁴² The majority agree, however, that it is a rare condition if it exists at all. It might be well to direct attention to the difficulties which Welch,⁴³ Doehle,⁴⁴ and Heller⁴⁵ encountered when they first described changes in the aorta as characteristic of syphilis. For many years the failure to find spirochetes in the aorta was used as an argument against the specificity of the lesions before these lesions were universally accepted as characteristic of syphilitic invasion of the aorta.

It impresses me as being rather unfortunate that the discussion of syphilis of the myocardium has centered around the question as to whether or not a specific form of myocarditis other than the gummatous type occurs. A care-

ful study of the excellent review by Saphir³⁶ obviously discloses that gummatous changes of the myocardium have been reported in many instances. This author in the beginning of his discussion stated that gummatous changes would not be reviewed. However, in 138 chronological case reports which he had reviewed, there were 66 instances in which reference to gummatous changes was made. Recently Sohval⁴⁶ stated that "the acquired tertiary syphilitic disease of the heart (exclusive of syphilitic aortitis with commissural involvement) is infrequent. If one omits from consideration the controversial diffuse fibrous type, the disease may be said to assume the form of diffuse interstitial gummatous myocarditis or that of localized gummatous myocarditis."

Syphilis may affect the coronary arteries either by involving the ostium of the main branch or by producing an endarteritis of the terminal branches. Pincoffs and Love⁴⁷ have recently emphasized the importance of occlusion of orifices of the coronaries in cardiovascular syphilis. In their small series of syphilitic aortitis 71.4 per cent dying a cardiac death showed this lesion. Love and Warner⁴⁸ in a study of syphilis of the heart, coronary ostia and coronary arteries concluded that the lesion of the coronaries most commonly noted was an obliterative endarteritis of the arterioles and that stenosis of the coronary ostia produces the most marked myocardial lesion. They also believe that the myocardial lesions in syphilitic aortitis can be attributed to defective coronary circulation. It is well to direct attention to the fact that, when the ostium of the coronary artery is entirely occluded by syphilis and infarction results, the infarction in no way differs from that associated with arteriosclerosis.

While syphilis of the myocardium is uncommon, there are clinical reports (Brooks,^{49, 50} Coombs,⁵¹ Carter and Baker,⁵² Blackford and Boland,⁵³ Magill⁵⁴) which suggest that it occurs more frequently than pathological studies indicate. If additional methods of study of the myocardium could be found and if more consideration were given to changes affecting the coronary arteries and to gummatous changes, it is possible that the pathologists and clinicians would be more in accord.

I have reviewed all the cases that I can find of syphilis of the myocardium since 1918, the time when Herrick⁴ directed attention to the clinical picture of myocardial infarction, and have been unable to find any reported cases of syphilis of the myocardium with electrocardiographic and pathological studies and findings that resemble the picture of infarction of the myocardium, with the exception of two instances occurring in the Massachusetts General Hospital. The first patient,⁵⁵ a male of 58 years of age, who had had a long anginal history, suddenly died following severe precordial pain. Coronary sclerosis and cardiac infarction were diagnosed. Autopsy showed "the ostium of the right coronary artery completely blocked by a gummatous process. No thrombosis of the coronaries or large infarction of the myocardium was found, however, numerous small fibrous scars were present in the myocardium, particularly in the interventricular septum. The histology of these suggests a luetic process rather than the ordinary fibrosis following circulatory block."

The second instance,⁵⁶ a male of 26 years of age, had an interesting history of three admissions over an eight months' period, in the first admission for jaundice the diagnosis was catarrhal jaundice, in the second because of severe, non-localizing pain and jaundice, a diagnosis of cirrhosis of the liver was made and in the third because of severe precordial pain the condition was diagnosed

as syphilitic heart disease. Autopsy findings supported this last antemortem diagnosis by revealing syphilitic cardiac lesions including myocarditis.

Langeron⁵⁷ reported an interesting case in which the clinical picture of myocardial infarction was present. However, with the final episode no electrocardiographic studies were reported. Autopsy revealed closure of the ostium of the coronary artery. No evidence of infarction was found.

The age of my patient, the history of syphilis, and later skin manifestations justified the opinion that the myocardial damage was associated with syphilitic lesions involving the orifice of the coronary artery and this was the diagnosis on the second day of admission. However, the course and the duration of the illness made the diagnosis unlikely and consequently the final diagnosis was acute myocardial infarction due to coronary thrombosis.

The case is of interest because at autopsy no occlusion of the coronary arteries was found. However, microscopic studies disclosed definite myocardial damage associated with gummata. Careful search for spirochetes in the heart muscle gave negative results. These findings are significant and important because all the symptoms, signs, laboratory and electrocardiographic evidence considered characteristic of myocardial infarction were present. Of special interest in this case are the electrocardiographic findings relative to the R T and S T changes which were of the type usually considered characteristic of myocardial infarction. The autopsy findings support the clinical and experimental observations,^{58, 59, 60, 61, 62} that the R T and S T changes in the electrocardiogram are associated with disturbance of the myocardium.

SUMMARY

A case of acute gummatous myocarditis simulating myocardial infarction is presented. The history, physical examination, laboratory findings, electrocardiographic evidence and clinical course usually considered characteristic of acute myocardial infarction were present. The age of the patient, the history of syphilis, and the secondary skin manifestations justified the admission diagnosis of myocardial infarction from closure of the ostium of the coronary artery due to syphilis, however, because of the duration of the illness the final antemortem diagnosis was acute myocardial infarction due to coronary thrombosis. The autopsy revealed patent coronary arteries, and active granulomatous myocarditis with multiple caseating foci.⁶³ No spirochetes were discovered in the heart muscle. The patent coronary arteries and the extensive myocardial involvement support the theory of the myocardial origin of the R T and S T changes which were found in the electrocardiogram. It is suggested that gummatous myocarditis probably occurs more commonly than has been realized, and that it has not been recognized because too much attention has been given to the yet not generally accepted specific interstitial myocarditis of Warthin. Gummatous myocarditis is presented as another condition to be differentiated in the diagnosis of myocardial infarction.

CONCLUSION

1 While the diagnosis of coronary thrombosis is usually not difficult, occasionally errors are made.

2 Review of the literature reveals that there are conditions which closely simulate coronary thrombosis.

3 Whenever the clinical picture of myocardial infarction occurs in a young person who has a history or signs of syphilis, the possibility of syphilis affecting the ostium of the coronary arteries or the myocardium should be carefully considered

4 Evidence is presented to support the theory that the R T and S T changes in the electrocardiogram indicate disturbance of the myocardium

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A CASE OF PERNICIOUS ANEMIA AND CHRONIC LYMPHATIC LEUKEMIA ¹

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THE combined occurrence of leukemia and pernicious anemia in one individual is undoubtedly rare. In 1900, Leube observed a patient with findings suggestive of both conditions, to which he gave the name "leukanamie." Since then a number of such cases have been reported, chiefly in the German literature. Sinek and Kohn ¹ in 1930 reviewed the reported cases and came to the conclusion that most of them were either a true leukemia with a macrocytic type of anemia, or pernicious anemia with a leukemoid (myeloid) white cell picture. They described a case which they had followed for two and a half years, in which they had made a diagnosis of myeloid leukemia superimposed on a pre-existing pernicious anemia. However, their evidence for the diagnosis of pernicious anemia is not conclusive. While their patient presented a macrocytic anemia, glossitis, increase in serum bilirubin and achlorhydria, no reticulocyte response was recorded and there was only a slight gain in the red count following liver therapy. Beiglbock ² reported a case of subleukemic myeloid leukemia

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with a clinical picture of pernicious anemia, and also reviewed the literature on the subject. The same objection may be raised to the diagnosis of pernicious anemia in his case as in that of Sinek and Kohn.

We wish to report a case recently studied at the Cincinnati General Hospital in which we feel the diagnosis of both chronic lymphatic leukemia and pernicious anemia is fully justified.

CASE REPORT

The patient, a white male, aged 75, was admitted to the Medical Service of the Cincinnati General Hospital on March 15, 1934. He had been in fairly good health until one year before, when he developed an aching pain in his back, shoulders and thighs, which became progressively worse. He had also noticed increasing weakness and dyspnea on exertion, and more recently some edema of the ankles. His appetite had been fairly good and he had been partaking of an adequate diet, particularly as regards meat and green vegetables. He had not lost weight. There had been some tingling and numbness of the extremities. He had noticed some enlargement of the lymph nodes on the right side of his neck for the past 15 years, but had not been conscious of any recent increase in their size. His general health had been good. In 1927 he underwent an appendectomy for chronic appendicitis in another hospital. No blood counts were recorded at that time. The remainder of the history was not significant.

Physical examination revealed an elderly man, with white hair and a sub-icteric tint to the skin and sclerae. There were no manifestations of purpura. Definite pallor was present. The fundi showed moderate vascular sclerosis and old focal chorioretinitis in the right eye. There was some congestion and edema of the nasal mucosa. The teeth were worn and pyorrhea was present. The tonsils were small and atrophic. The tongue was pale, clean and somewhat smooth around the edges, the papillae were not definitely atrophied. The thyroid was not remarkable. A generalized lymphadenopathy was present, with involvement of the cervical, submaxillary, supraclavicular, infraclavicular, axillary, epitrochlear and inguinal nodes. The glands varied in size from that of a pea to a walnut. They were discrete, firm, not tender and freely movable. The lungs were not remarkable except for moderate senile emphysema. There was no cardiac enlargement as determined by percussion or roentgen-ray. A systolic murmur was heard along the left sternal edge. The rhythm was regular, and the sounds were distant. The peripheral vessels were moderately thickened. The blood pressure was 120 mm of mercury systolic and 85 diastolic. The liver extended 8 cm below the right costal margin, it was firm, smooth and presented a sharp edge. The spleen extended 6 cm below the left costal margin and was firm and slightly tender. No other abdominal masses were felt. A midline ventral hernia was present. There was moderate soft pitting edema of the ankles. The deep reflexes were absent. Position sense was intact. Vibratory sense was absent over the lower extremities. Rectal examination was negative.

The results of various laboratory examinations on admission were as follows. There were 1,200,000 red cells and 40 per cent hemoglobin (Sahli). The white count was 85,800 and the differential smear showed 93 per cent lymphocytes of varying ages, 5 per cent monocytes and 2 per cent neutrophils. The red cells showed poikilocytosis and macrocytosis. The mean corpuscular volume was 111, mean corpuscular hemoglobin 39.8 and mean corpuscular hemoglobin concentration 36.1. The platelets were apparently reduced in number. The urine was negative except for a trace of albumin, which later disappeared. A gastric analysis showed no free HCl following the injection of $\frac{1}{2}$ mg. of histamine, and a total acidity of 6. The Kahn test on the blood was negative. The clotting and bleeding times were normal. The icteric index was 9.7 and the serum bilirubin gave an indirect Van den

Bergh reaction There was no retention of bromsulphalein $\frac{1}{2}$ hour after a dose of 2 mg per kilogram of body weight. The serum protein was 5.71 grams. The non-protein nitrogen of the blood was 26 mg per cent.

The clinical picture together with a white cell count of 85,800, of which over 90 per cent were lymphocytes, established the diagnosis of chronic lymphadenosis (chronic lymphatic leukemia). Because of the high color index and the presence of many macrocytes, it was felt that the patient was also suffering from pernicious anemia. This was further borne out by the histamine achlorhydria, the lack of vibratory sensation over the lower extremities and the hematocrit values.

Accordingly, treatment was begun with liver extract intramuscularly. He was given a total of seven injections, each derived from 100 grams of liver, over a period of 9 days. The reticulocytes, which had varied between 1.5 per cent and 2.5 per cent, began to rise 7 days later, and within two days reached a peak of 16.5 per cent (chart 1). They then fell rapidly to the pre-treatment level, which was reached in 18 days. Further treatment consisted in the administration of 30 grams of Ventriculin daily.

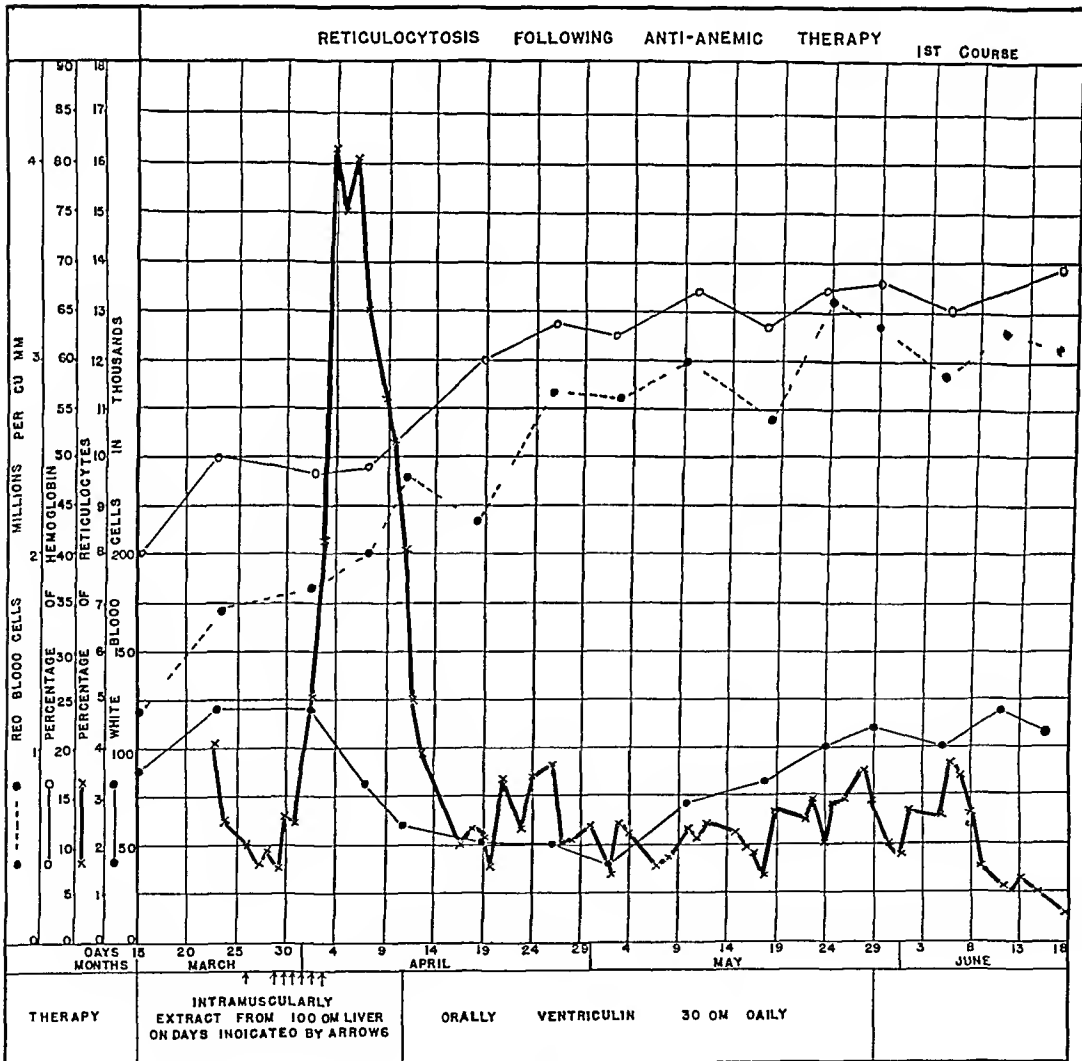


CHART 1

The red count rose gradually from 1,700,000 on March 28, to reach a maximum of 3,300,000 on May 24. There was a corresponding increase in the hemoglobin from 50 per cent to 68 per cent during the same interval. During the remainder of this period of treatment, the reticulocytes varied between 15 per cent and 37 per cent. The white count during this period fell gradually from 120,000 to 40,000 and then rose to 110,000. The differential blood picture continued to show a predominance of old and young lymphocytes. After three weeks of treatment, however, there occurred a small increase in the percentage of neutrophils, and later there was a transient rise in eosinophiles, which numbered 7.5 per cent on March 27.

In order to rule out coincidence, it was decided to see if a reticulocyte response could be obtained a second time. Accordingly, all anti-anemic therapy was discontinued for a period of eight weeks, during which time the bone marrow showed little erythropoietic activity. Almost daily reticulocyte counts varied between 0.5 per cent and 1.5 per cent. The red count dropped to 1,800,000 and the hemoglobin to 44 per cent. The white count rose to 230,000 with over 95 per cent lymphocytes. On August 22, treatment with anti-anemic substances was resumed. Extract derived from 300 grams of liver was given intramuscularly during a period of one week, in

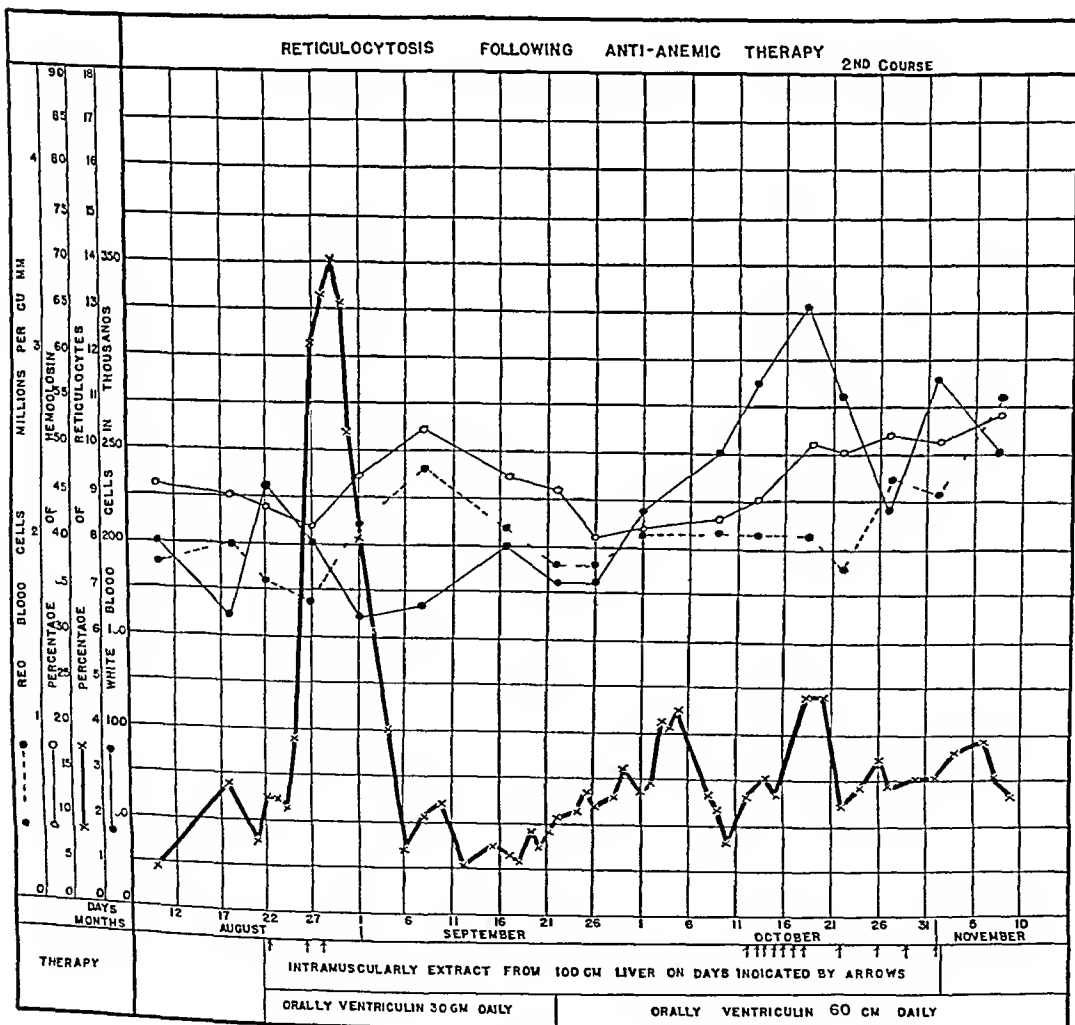


CHART 2

TABLE I
Partial List of Blood Counts (Almost Weekly Intervals)

Date	R B C (Mill.)	Hgb (Sahli)	W B C (Thous.)	Lymphs %	Mon %	Pmn %	Eos %	Bas %	Lymphobl %	Remarks
1934										
3-15	12	40	85.8	100.0	0.0	0.0	0.0	0.0	0.0	
3-28	17	50	120.0	99.0	0.0	1.0	0.0	0.0	0.0	7 injections 3 c c liver extract
4-2	18	48	120.0	95.0	0.0	5.0	0.0	0.0	0.0	
4-7	20	49	80.0	95.5	0.5	4.0	0.0	0.0	0.0	
4-11	24		60.0	88.5	0.0	11.0	0.5	0.0	0.0	Ventriculin, 30 gm daily
4-19	22	60	50.4	90.5	1.0	7.5	1.0	0.0	0.0	"
4-26	28	63	50.0	76.0	1.5	12.0	7.5	0.0	3.0	"
5-2	28	62	40.0	89.5	1.5	7.0	2.0	0.0	0.0	"
5-10	30	67	70.0	93.5	0.0	3.5	0.0	0.0	3.0	"
5-18	27	63	80.0	94.5	0.0	4.0	0.5	0.0	1.0	"
5-24	33	67	100.0	87.5	1.5	10.0	0.5	0.0	0.5	"
5-29	32	68	110.0	91.0	0.0	4.5	2.5	0.0	2.0	"
6-5	29	65	110.0	86.5	1.0	7.0	5.5	0.0	0.0	No treatment
6-11	32	67	120.0	94.5	0.5	2.0	1.0	0.5	1.5	"
6-16	31	69	110.0	96.0	0.5	3.0	0.5	0.0	0.0	"
6-22	31	61	130.0							"
6-28	31	63	90.0	96.5	0.0	1.0	1.5	0.0	1.0	"
7-5	25	58	145.0							"
7-12	23	55	190.0							"
7-17	26	60	200.0	95.5	0.0	1.5	2.0	0.0	1.0	"
7-27	24	52	150.0							"
8-10	19	46	200.0	97.0	0.0	1.0	0.5	0.0	1.5	"
8-18	20	45	160.0							
8-22	18	44	230.0							3 injections 3 c c liver extract
8-27	17	42	200.0	96.5	0.5	1.0	0.5	0.0	1.5	Ventriculin, 30 gm daily
9-1	21	47	160.0	91.0	0.5	5.0	2.0	0.0	1.5	"
9-8	24	52	166.0							"
9-17	21	47	200.0	92.5	1.0	3.5	3.0	0.0	0.0	"
9-22	19	46	180.0							"
9-26	19	41	180.0	99.0	0.0	0.5	0.0	0.0	0.5	"
10-1	21	42	220.0	98.5	0.0	0.5	0.5	0.0	0.5	Ventriculin, 60 gm daily until death
10-9	21	43	250.0	93.5	1.0	3.0	1.0	0.0	1.5	
10-13	21	45	290.0	94.5	0.0	2.5	2.0	0.0	1.0	11 injections, 3 c c liver extract
10-18	21	51	330.0	97.0	0.0	1.0	1.0	0.0	1.0	
10-22	19	50	280.0	96.0	0.5	1.0	1.0	0.0	1.5	
10-27	24	52	220.0	97.0	0.0	3.0	0.0	0.0	0.0	
11-1	23	51	290.0	95.0	0.5	2.5	0.0	0.5	1.5	
11-7	28	54	250.0	95.5	0.0	3.5	0.5	0.0	0.5	
11-12	26	53	240.0	98.5	0.0	1.0	0.5	0.0	0.0	
11-19	25	53	270.0	98.5	0.0	1.0	0.0	0.0	0.5	
11-26	24	49	230.0	94.5	0.5	2.5	0.5	0.0	2.0	3 c c liver extract
12-6	23	47	30.0	94.0	0.5	5.0	0.5	0.0	0.0	X-ray therapy
12-12	22	47	40.0	92.5	0.0	6.0	1.0	0.5	0.0	
12-28	26	52	90.0	97.0	0.5	1.5	0.0	0.0	1.0	
1935										
1-7	20	48	3.4	74.0	0.0	21.0	4.0	1.0	0.0	
1-24	19	41	5.0	79.0	2.0	18.0	1.0	0.0	0.0	
2-14	19	43	5.7	77.0	9.0	5.0	8.0	1.0	0.0	
3-4	21	46	44.3	88.0	0.5	10.0	1.0	0.0	0.5	

addition to 30 grams of Ventriculin daily. A rise in the reticulocytes again occurred, beginning on the third day and reaching a maximum of 14.1 per cent on the seventh day and returning to the pre-treatment level on the seventeenth day (chart 2). The red count and hemoglobin did not increase as much as before, reaching a level of 2,400,000 and 52 per cent respectively after three weeks. The increase was not maintained, and by the end of September the values had fallen to 1,900,000 and 41 per cent respectively. The dosage of Ventriculin was then increased to 60 grams a day, and in October he was given 11 injections of liver extract. This produced a slight prolonged reticulocytosis and later an increased red count and hemoglobin, the red cells reaching 2,800,000 and the hemoglobin 54 per cent on November 7. The white count did not fall during this second course of treatment, but ranged between 160,000 and 330,000.

An attempt was made to demonstrate the presence or absence of the intrinsic substance in the patient's gastric juice by incubating it with material containing the so-called "extrinsic" factor, but sufficient quantities of gastric juice could not be obtained.

The patient was given 60 grams of Ventriculin daily for the remainder of his illness. The red count gradually fell to 1,900,000 and the hemoglobin to 41 per cent. In December and again in January 1935, he received roentgen-ray therapy over the spleen and cervical nodes, which resulted in a marked drop in the number of white cells.

It is to be noted that the first reticulocyte response was slightly delayed, and submaximal, considering the large amount of potent material given, and that the red count and hemoglobin never reached normal levels. We believe that this may be explained by the fact that the bone marrow was so infiltrated with leukemic tissue as to obviate a normal response. Nevertheless, the red cell count and hemoglobin were increased to the level usually seen in leukemia in an advanced stage.

The patient remained in the hospital until his death one year later. During his stay almost daily studies were made of his blood. Some of these are recorded in table 1. His general condition remained about the same, except for signs of myocardial weakness, until late in February 1935, when he developed a purulent otitis media. Soon after this he contracted pneumonia, which proved fatal on March 6, 1935. Autopsy was performed four hours after death by Dr. James Mack.

The significant findings at necropsy were as follows. There was a generalized lymphadenopathy involving the cervical, infraclavicular, epitrochlear, axillary, inguinal, femoral, mediastinal and abdominal nodes. The glands were soft and yellow in color, and frequently as large as walnuts. There was some myocardial degeneration and fibrosis. The liver weighed 2580 grams, and presented numerous very small nodules on its surface. On section there was a large amount of yellow mottling. The spleen was likewise enlarged, weighing 625 grams. It was soft, with a tense capsule and a smooth uniformly pale red pulp. Microscopically, the lymph nodes were filled with a solid mass of small lymphocytes which completely destroyed the internal structures. There was also evidence of leukemic infiltration of the viscera. The spinal cord showed degenerative changes which were most marked in the posterior and lateral columns. Sections of the bone marrow showed lymphoid infiltration replacing to a great extent the myeloid elements. The erythropoietic centers presented a small number of megaloblasts, as well as normoblasts. Macrocytes were present in every field. The prostate, although grossly not remarkable, gave microscopic evidence of a chronic interstitial prostatitis and an early adenocarcinoma. Lobar pneumonia was present in the left lower lobe and confluent lobular pneumonia in the left upper and right lower lobes.

We believe that the diagnosis of chronic lymphatic leukemia in the case reported cannot be questioned. The enlarged spleen, enlarged lymph glands, per-

sistently high white count with predominance of lymphocytes and the anatomic changes are all typical of this disease. The diagnosis of pernicious anemia is also warranted in view of (1) the macrocytic anemia which responded on two occasions with a rise in reticulocytes and an increase in the red count and hemoglobin after the use of "specific" anti-anemic therapy, (2) achylia gastrica, (3) loss of vibratory sense and (4) degeneration of the posterior and lateral columns of the spinal cord.

No attempt is made to correlate the etiology of these two conditions by the study of this case. In all likelihood, the existence of the two diseases in the same individual was a coincidence.

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LIPEMIA ACCOMPANIED BY ATHEROMATOUS AND OCCLUSIVE VASCULAR DISEASE. REPORT OF A CASE AND PARTIAL REVIEW OF THE LITERATURE *

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ACCORDING to Rowland and to Pick, the disorders of lipid metabolism may be classified as essential or primary, and symptomatic or secondary. Among the primary disturbances Rowland considered essential xanthomatosis, with involvement of skin, mucous membranes, tendon sheaths, or viscera, Niemann-Pick disease, Schuller-Christian disease, and Gaucher's disease. As Rowland said, there are cases that defy classification.

The group under present consideration is that which Pick described as the residual group, Rowland as essential xanthomatosis. There is in this group no characteristic age, sex, or racial distribution. The clinical manifestations are extremely varied. There are a number of cutaneous types, varying from the small xanthelasma palpebrarum to general eruptive forms. The mucous membranes may be involved, as in the cases of Finney, Montgomery, and New. They reported from The Mayo Clinic two cases of xanthoma multiplex involving the larynx and trachea, associated with diabetes insipidus. Small subcutaneous xanthomas may occur, and rarely, larger xanthomas may occur as tumors on tendon sheaths and aponeuroses. Visceral involvement of varying extent and location may also occur. In some cases vascular involvement may be the chief manifestation.

These various manifestations may be observed separately or in various com-

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binations The characteristic histologic feature of this group of cases is the presence in the involved regions of large, clear, foamy cells containing lipids, in which cholesterol and its esters usually predominate The lipids in the blood may be normal or elevated, and if elevated there is practically always hypercholesterolemia Robertson and Warlen reported a case in which the diagnosis depended on biopsy of a lymph node, the deposits of lipid occurred principally if not entirely in the lymph nodes, and the lipids in the blood were not increased

Investigations have revealed a large number and wide variety of conditions in which a disturbance of the lipids is found as a symptomatic or secondary manifestation Even excitement may produce temporary hypercholesterolemia, Lyons found this to be abolished in cats by sympathectomy

Prolonged obstruction of the biliary tract produces an increase in the level of cholesterol in the blood Gardner and Gainsborough reported this to be true in a case of obstructive jaundice, in a case of stone in the common duct, and in a case of carcinoma of the pancreas and gall-bladder with biliary obstruction Hypercholesterolemia was observed in a case of obstructive jaundice reported by Brain and Byrom, and in cases of subacute yellow atrophy and subchronic atrophy of the liver reported by Adler and Lemmel Similar changes occur in most stages of catarrhal jaundice

An increase of cholesterol and cholesterol esters in the blood often is found in renal disease, notably nephrosis, in two such cases Lichtenstein and Epstein found exceedingly high levels for cholesterol In cases of acute nephritis, Maxwell found the increase in cholesterol to be proportional to the amount of edema, he observed high values for cholesterol in cases of chronic nephritis with or without edema Ashe and Bruger found high values for cholesterol in cases of chronic glomerulonephritis, in some of which the value for urea in the blood was normal, in others elevated Hurxthal, and also Myers, found an increase in the cholesterol in the blood of patients with extensive arteriosclerosis Westphal found that 71.2 per cent of eight patients with hypertension had high values for blood cholesterol, and this was true even in early life

High values for blood cholesterol may also be observed in cases of diabetes mellitus Oppenheimer and Fishberg observed that "The old blood-letters were well aware that under certain conditions, notably severe diabetes mellitus, the blood may contain an excess of fat so great that, on being left to stand, a thick creamy layer separates to the top" Jaffe, Morris, and Schonfeld have reported a case of lipemia retinalis in a diabetic with marked hyperlipemia Lepard reported a case of diabetes with well-marked hyperglycemia and hyperlipemia, cutaneous xanthomas, and lipemia retinalis Curtis, Sheldon, and Eckstein observed that, to have a severe lipemia, the diabetes must be severe, and that the lipemia disappears under control Collins has said that high values for blood fats, and Rabinowitch that high values for blood cholesterol, indicate an unfavorable prognosis in cases of diabetes

Hurxthal stated that, in myxedema, the percentage of increase of cholesterol in the blood is so much greater than the percentage of decrease in the rate of metabolism that the value for cholesterol stands out as an indicator of thyroid deficiency Mason, Hunt, and Hurxthal reported the observation of a series of cases with high values for cholesterol in the blood

Kumpf found that prolonged bleeding leads to persistent lipemia in rabbits Muller found that, regardless of the severity of the anemia, the initiation of a

remission in cases of pernicious anemia is characterized by a sudden increase in blood cholesterol, which during relapse was below normal

Sternberg found increased values for cholesterol in the blood of patients with manic depressive insanity, and Huxthal concluded that hypercholesterolemia is more frequent among patients with mental disease than among those with general disease. McQuarrie, Husted, and Bloor concluded regarding epileptics that "a relative increase of plasma lecithin favors the occurrence of seizures, while a relative increase in cholesterol tends to prevent them." In a study of 100 epileptic and 32 nonepileptic children, McQuarrie, Bloor, Husted, and Patterson found no significant difference in the range of values for plasma cholesterol or in its variability in the two groups. Rosen, Krasnow, and Notkin found that the average values for the cholesterol and lecithin content of the blood in epilepsy were normal.

Rosen and Krasnow observed that, in general, the cholesterol content of whole blood tends to be high in dermatoses. In pregnancy, according to McEachern and Gilmour, cholesterol is increased, particularly in the last trimester. Diets rich in fat, such as the ketogenic diet, lead to an increase in the level of lipids in the blood. Bruger and Poindexter found normal lipid levels in obese individuals without complicating diseases. Prolonged starvation is said by McEachern and Gilmour to lead to an increase of cholesterol in the blood.

An abundant literature confirms the fact that the feeding of diets rich in cholesterol is followed in animals by the formation of atherosclerotic lesions in various vessels. Ignastovskii, in 1908, observed atheromas in the aortas of rabbits after feeding them milk and egg yolks, and this observation was confirmed in 1909 by Starokadomsky and Ssobolew, who found similar changes in the innominate carotid, and subclavian arteries. Anitschkow and Chalutow concluded that cholesterol was the substance responsible for these changes, and in 1913 they produced, by the feeding of pure cholesterol to experimental animals, an aortic sclerosis similar to that observed in man.

Anitschkow, in 1924, found that local vascular changes may be produced in the absence of large increases of lipids if the vessel be traumatized. Whether, as Harris and Lipkin have said, these observations are applicable to man is another question. Leary has observed that man is the only animal that ingests eggs and milk during a lifetime, and man is the only animal that dies in early life from coronary sclerosis and acquires atherosclerosis almost universally in advanced years.

There are a number of reported instances of atheromatous or xanthomatous infiltration of the cardiovascular system in a variety of conditions associated with elevated levels of lipids in the blood. Fagge in 1873, reported the occurrence of xanthomatous infiltration of the left auricle, aorta, and pulmonary, innominate, and carotid arteries of a patient who had long suffered from obstructive jaundice and had numerous cutaneous xanthomas. In the same year Maxon reported the observation of atherosclerosis in a patient with hepatic cirrhosis and cutaneous "xanthelasma." A girl of 11 years, who had cutaneous xanthomas, was examined by Lehzen and Knauss who in 1889 reported that they found yellow raised patches on the mitral valve, producing incompetence, similar changes were observed in the aorta and pulmonary, coronary, and left carotid arteries. Pollosean, in 1890, and Low, in 1910, observed precordial murmurs

in patients who had xanthomas on the skin, but necropsy was not performed in either instance

In 1925 Oppenheimer and Fishbein observed atherosclerotic areas containing large "foamy" cells in the cardiovascular system of a patient who had had papular xanthomatosis and who had died in diabetic coma, similar changes were found in two cases reported by Lutz in 1914. Knox in 1919 observed in a case of Gaucher's disease rows of swollen granular cells, similar to those in the spleen, surrounding the musculature of some of the small arterial twigs. Siegmund in 1921 noted in a case of Gaucher's disease that the endothelium of vessels in the skin, heart, and kidneys contained large lipid cells. Benda in 1924 described the occurrence of xanthomatosis of the pulmonary veins in a case of nephrosis with marked lipidemia. Velhagen in 1914 reported a case of hemorrhagic glaucoma in which there were large clear cells between the endothelium and internal elastic membrane of the central artery of the retina.

CASE REPORT (ABRIDGED)

The patient in the present case a married woman, aged 55 years, came to the Clinic May 7, 1934, complaining principally of weakness, exhaustion, spots before her eyes, and of headache. Her father had died of apoplexy, but the family history was otherwise negative. One of her children was living and well, one had petit and grand mal. The patient had been rather high-strung, had worried greatly, and had had morning headaches for at least 10 years. She had had insomnia and hot flashes for four or five years, but, until 1932, had considered herself in good health.

In August 1932, the patient had not felt well. Some cardiac weakness and a systolic blood pressure of 200 mm. of mercury were found. She had kept moderately quiet. In November 1932, she had suffered much fatigue and pounding in the head and had stayed in bed much of the time during the next four months. The metabolic rate had been normal. In bed, the blood pressure had fallen to 148 mm. of mercury. In June 1933, vertigo suddenly had developed, necessitating rest in bed, this had lasted until fall. In December 1933, the patient suddenly had become blind in the left eye for 15 minutes, and later had had scotomas of various kinds before both eyes. In February 1934, a similar attack had occurred, and she had seen vari-colored lights for two days, at times there had been hemi-vision. Later she had had a feeling as if someone were sitting on her chest, this had been accompanied by discomfort in, and slight disuse of, the left hand. There had been moderate dyspnea on exertion. The history otherwise was not significant.

At the time of examination the patient was found to have a mild elevation of systolic and diastolic blood pressure. On deep inspiration the liver edge was felt hard and sharp one inch (2.5 cm.) below the umbilicus in the mammary line. There was sclerosis, grade 1+, of the retinal arteries, of the hypertensive type, exaggerated disk rings, and mild choroidal degeneration in the region of the maculae. There was no evidence of lipemia in the retinal vessels. Three specimens of urine showed no significant abnormality. Serologic test of the blood for syphilis was negative. Roentgenograms of the head and of both humeri were negative, and those of the lumbar portion of the spine, pelvis, and upper ends of the femurs revealed hypertrophic changes in the lower thoracic and upper lumbar portions of the spinal column but otherwise no structural changes in bone. A roentgenogram of the thorax revealed only slight cardiac enlargement. The value for cholesterol was 667 mg. per 100 cc. of plasma, total fatty acids being 1971 mg., and total lipids 2638 mg. The basal metabolic rate was +8 per cent. Electrocardiograms were normal save for diphasic T-waves in derivations I and II and iso-electric T-waves in derivation III.

Tests of liver function by the Rowntree-Rosenthal method showed the presence of dye in the serum at the end of one hour, it was impossible to determine the degree of retention of dye owing to the high grade lipemia. Total values for lipids in the urine were 22 mg per 100 c c, in a total of 1115 c c of urine constituting a 24 hour specimen. Neurologic examination strongly suggested some cerebral or retinal vascular spasm with residual scotomas, but the neurologic findings were extremely few.

A diagnosis was made of moderate hypertension, arteriosclerosis of the central nervous system and coronary arteries, general arteriosclerosis, moderate enlargement of the liver, cardiac hypertrophy, and lipemia of unknown origin. Because of the unexplained lipemia, together with the absence of significant changes in bony structures, the suggestion of essential xanthomatosis was made and a diet low in fat was recommended.

The patient was permitted to return to her home, where, at our suggestion, a test of sugar tolerance was made, a diabetic type of glucose tolerance curve was obtained. She was given a rather high carbohydrate diet with limitation of fats. Insulin was administered for a time but its use was discontinued because of untoward effects.

The patient returned to the clinic August 2, 1934, she had lost 19 pounds (8.6 kg) and had gradually become weaker. There was weakness but not paralysis of her entire left side, which at times had felt numb, it had tingled and prickled. Sometimes it had been difficult to articulate. The patient gave evidence of loss of weight, but she did not appear acutely ill. There was mild hypertension and the peripheral vessels were sclerotic, grade 2. The heart was slightly enlarged, the liver was palpable on deep inspiration, three fingers' breadth below the costal margin. Gross examination of the eyes gave essentially negative results. The neurologist thought that, on the basis of the complaints referable to the central nervous system, the symptoms were probably on an arteriosclerotic basis.

One week after admission the patient complained of feeling dizzy and of weakness of the left side of her body. Shortly thereafter complete motor paralysis of the left side developed, including the external ocular muscles, together with great difficulty in swallowing and speaking. Spinal puncture revealed nothing abnormal. The most likely diagnosis seemed to be cerebral and pontine thrombosis, although brain tumor or hemorrhage could not be excluded. Because the lesion might be a xanthoma, four roentgen treatments of the brain were given on four successive days. For a short time the patient was given 50 gm of fat per day, but later fat consumed varied from 6 to 50 gm each day. The total daily caloric intake varied from 875 to 1890 during the period of hospitalization. There was gradual improvement of the patient's eyes, speech, and limbs.

Roentgenograms of the head, spinal column, and pelvis revealed no significant changes. Tests of liver function did not reveal retention of dye. There were 30 mg of urea and 81 mg of glucose per 100 c c of blood. Glucose tolerance was normal. All values for plasma lipids are indicated in table 1. Twenty-five days after this admission the glucose tolerance again was found normal.

The patient returned October 2, 1934. After leaving the hospital in August she had improved rapidly for two weeks, after two weeks the improvement had been more gradual. About 10 days before this admission she had had "trembling" in the abdomen, which had been generalized and intermittent, and about the same time she had noticed increased nervous tension, which had persisted. There had been occasional aching in the left arm, and once, a severe pain in it. In the last week she had had a sensation of pressure over the left part of her chest, which had not been accompanied by pain or cardiac palpitation. Her left hand was hypersensitive to heat, the fingers were still somewhat stiff and "felt full." There had been edema of the left hand since the onset of hemiplegia. She had gained 15 pounds (6.8 kg) in the month prior to this admission.

On examination, there was moderate pallor of the skin and mucous membranes, the pupils reacted to light. The heart was slightly enlarged to the left, the tones were good and murmurs were absent. There was peripheral sclerosis, grade 2, and a mild hypertension. The liver edge was palpable three fingers' breadth below the costal margin in the midclavicular line. The spleen was not palpable. There were no abdominal masses and no enlargement of the lymph nodes. There was abortive nystagmus on looking to the left, and slight left facial weakness. Deep reflexes were hyperactive on the left side. There was a positive Hoffman sign in the left hand, but a negative Babinski reflex. Abdominal reflexes were not elicited except in the left lower quadrant, which was hyperactive, grade 2.

The eyes were essentially the same as on the previous visit except for improvement in the strength of the muscles. Four specimens of urine were essentially negative. The values for hemoglobin and the erythrocyte and leukocyte counts were normal, values for lipids in the blood are given in table 1, those for blood urea and sugar were within normal limits. The electrocardiogram was normal save for diphasic T-waves in derivation I. The increase in blood fats despite the low fat diet could not be entirely explained, but it was thought best to continue the diet with the low fat content. For five nights in succession the patient had attacks of severe precordial pain, radiating to the left arm. She of course had not exercised and thought that the pain was not related to excitement. She did state that the pain came on after eating. Physical examination of the heart revealed no abnormality, but, because of the history and the diphasic character of the T-wave in derivation I in the electrocardiogram, it was thought that the attacks were probably anginal in origin. About this time it was thought advisable to lower the caloric content of the diet to 550 each day, the intake of vitamins and minerals was supplemented by giving brewer's yeast (Harris), proprietary tablets of vitamins A and D (Adex), and calcium phosphate.

Although an initial rise in cholesterol occurred on the fourth day, there was a rapid diminution in the fatty acids and total lipids (table 1). There was, however, little subjective improvement in the patient's condition and she continued to have

TABLE I
Lipid Values during Observation, Milligrams per 100 c c

	1934									
	5-11	8-4*	8-17	8-29	8-31	10-2	10-9	10-15	10-20	10-22
Cholesterol	667	354	278	333	416	454	567	430	302	387
Fatty acids	1971	530	666	986	1076	2732	1206	885		694
Total lipids	2638	884	944	1319	1482	3186	1773	1315	302	1081

Grams per day										
Diet while in hospital	8-2		8-12				10-5			10-22
Carbohydrate	300		275				57			261
Protein	60		55				49			100
Fat	50		25				10			21

* On this date, lecithin 371 mg per 100 c c, and cholesterol esters 231 mg per 100 c c of blood

some pain in her left shoulder and arm. October 16, there was an increased weakness of the left arm and leg, with a subjective sensation of numbness. There was definite impairment of speech and deglutition. A rather marked, vertical nystagmus developed, horizontal nystagmus was still present on rotation to either side, and the strength of the right external rectus muscle was still impaired. There was no change in the ocular fields or fundi. October 19 the patient's condition was sufficiently improved to permit further roentgen therapy, and each of four segmental regions of the head was irradiated, one each day. Since the patient still had difficulty with mastication and deglutition and was weaker, it was deemed advisable, on October 22, to increase the caloric intake to 1633, the fat was still markedly limited, to 21 gm daily. The carbohydrate allowance was 261 gm, the protein, 100 gm. Amino-acetic acid was given, one level teaspoonful four times daily.

In the next two days there was an appreciable improvement in the patient's condition, she felt much stronger and was able to sit up in bed for the first time in a week. On October 24 she felt particularly well, until about 6 p.m., when suddenly she had a severe and persistent pain in her left shoulder. This was controlled with some difficulty by opiates. After two hours the patient became unconscious, there was a gradual decline and she died.

Postmortem examination revealed extensive atheromatous changes in the arteries but no organic changes suggestive of any of the named lipid dyscrasias. The heart weighed 342 gm, and there was an increase in fat, grade 1+. At the base of the left ventricle, anteriorly and laterally and extending to the posterior surface, a region supplied by the circumflex branch of the left coronary artery, there was an area of softening, grade 3, of the myocardium. The circumflex branch of the left coronary artery was completely occluded by a thrombus (figure 1). Atherosclerosis, grade 3 to 4, of the coronary arteries was found, and there was atherosclerosis, grade 2, of the thoracic aorta.



FIG 1 Thrombus near origin of circumflex branch of left coronary artery, the atheromatous infiltration is easily seen

The liver extended 1 cm below the costal margin in the midclavicular line and weighed 1983 gm, the cut surface revealed an increase of fat, grade 2, and fat could be seen on the cutting knife. The gall-bladder contained four stones. The spleen weighed 200 gm and was slightly softened, the pancreas weighed 80 gm and revealed

fat replacement, grade 1 The splenic artery was very tortuous and gave evidence of atherosclerotic changes, grade 3 +, on cross section it appeared to be almost completely occluded There was atherosclerosis of the abdominal aorta, grade 3 to 4, with extensive atheromatous abscesses (figure 2)



FIG 2 Aorta, showing extensive atheromatous degeneration and formation of "abscesses"

The vessels of the brain showed extensive atherosclerotic changes, the basilar artery being completely occluded by sclerosis and thrombosis There was slight generalized atrophy of the brain, an infarct measuring 2 by 1 cm on the superior surface of the right lobe of the cerebellum, an infarct measuring 3 by 2 cm in the

posterior apex of the occipital pole of each cerebral hemisphere, an infarct 7 mm in diameter in the right superior olive, and a few small infarcts measuring up to 5 mm in diameter in the right side of the pons

Microscopic examination of the infarcted region of the heart revealed many islands of old and recent infarction, with dense connective tissue replacement in the old and pale-staining tissue and many leukocytes in the newly infarcted area. No intercellular or intracellular fat was seen in the heart except in the infarcted area. In the coronary arteries there was an eccentric intimal thickening, consisting of lipid material and cholesterol crystals. These changes varied in extent from small plaques to complete occlusion of the arteries, there was thrombosis in the region of the atheromatous abscess. In the left descending coronary artery there was complete occlusion and canalization (figure 3)



FIG 3 Left descending coronary artery, showing thrombosis, the lipid infiltration of the entire wall of this vessel is visualized—black staining areas—(low power)

The section of the spleen contained small infarcts. There were scanty lipid deposits in an occasional reticulo-endothelial cell, but no foam cells could be found. In the liver there was moderate congestion and some central atrophy. A fine, fat dust was scattered diffusely within the cells, here, too, no deposits of lipid could be demonstrated that were characteristic of any described lipid dyscrasia. The suprarenal glands showed a rather extensive deposit of lipid, the intracellular lipid being present as droplets. There were lipid-containing cells arranged in radial fasciculi, extending from the capsule through the reticular layer. The alternate bands revealed a fine intracellular fat dusting. The changes were not, however, as pronounced as those sometimes seen in presumably normal glands. The kidneys were essentially normal, although occasional fine lipid droplets could be seen in the collecting tubules and in the intima of the arterioles. The splenic artery revealed extensive atheromatous changes, with complete occlusion in some places. The lymph nodes revealed no abnormality and there were no significant changes in the bone marrow.

COMMENT

There was nothing about the condition of this patient to suggest Gaucher's disease. Schuller-Christian, Niemann-Pick, and Tay-Sach disease were readily excluded on the basis of the patient's age. We felt that the case probably would be best classified as one of essential xanthomatosis and we treated the patient accordingly. No condition other than moderate hypertension and arteriosclerosis was present in which disturbed lipid metabolism has been reported to occur as a secondary manifestation. We do not believe that the degree of hypertension observed in this case, particularly in the absence of significant renal changes, can be considered to be the factor responsible for the disturbed metabolism of lipid. Although one glucose tolerance test was characteristic of diabetes, we feel that the observation of normal levels of blood sugar, the absence of glycosuria, and a normal glucose tolerance response on two occasions exclude the diagnosis of true diabetes mellitus. It would, therefore, seem that this is best classified as a case of so-called "essential" xanthomatosis, with localization primarily in the vascular system. Despite the extremely advanced vascular changes, there were no significant lipid deposits in any other part of the body.

It is interesting in this connection to note the experimental evidence of production of atherosclerotic changes as a result of diets high in cholesterol. So far as we were able to determine, our patient had always adhered to a well-rounded dietary, the elevation in lipid would seem to have been on the basis of an anomaly of lipid metabolism. It seems most reasonable to postulate this as the primary and the atherosclerosis as the secondary manifestation, however, the possibility must be considered that the atheromatous changes in the arteries were primary and the lipemia due to rupture of atheromatous "abscesses."

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EDITORIAL

HEAT CRAMPS

IN recent years a considerable literature has sprung up in connection with the clinical condition which in the past has been called by various authors firemen's cramps, stokers' cramps, miners' cramps, cane cutters' cramps or mill cramps, and which is now usually designated by the more general name of heat cramps. This literature has been analyzed by Talbott¹ in a general review in which he includes also a presentation of his own studies in this field.

Heat cramps are a severe form of muscular cramps, occurring chiefly in the extremities, during or following heavy labor, at a high working temperature and in the hot season of the year. They are infrequently seen by the average physician but are well known to the industrial surgeons in the steel mills and in certain mines, as well as to ships' surgeons in the tropics.

These cramps are described as involuntary spasmodic contractions coming on either in isolated groups of muscles in the extremities, as for example in the flexors of the fingers, or affecting more widely the large muscles of the legs, of the arms, of the back or the abdominal wall. Even the facial musculature may be involved. The smooth muscles probably do not participate in the process.

In severe cases the cramps recur every few minutes, the interval lengthening as the attack wears off. The duration of the individual cramp is from one to three minutes and during this time the contracted muscles are stony hard or board-like. The pain is very severe in the stage of paroxysmal contraction but disappears in the interval. The duration of an attack of heat cramps may be from a few hours to several days.

As opposed to heat stroke and heat prostration, heat cramps present rather mild constitutional symptoms. There may be slight headache or vertigo. The temperature is within a normal range. The blood pressure shows no significant change. The pulse and respiratory rate are moderately increased. The severity of the pain in the severe cases may, however, seriously exhaust the patient. Death from uncomplicated heat cramps may occur.

Talbott has made an interesting study of the etiologic factors involved in the production of heat cramps. Foremost among these is the concurrence of a high working temperature and a high atmospheric temperature. In other words, it is in the season or in the geographic location where the worker is exposed to continuous high temperature that heat cramps are most frequent. In the steel mills of the Youngstown district more than 90 per cent of the hospitalized cases are admitted between April and October of each year. The temperature at which heat cramps occur is generally over

* TALBOTT, J. R. Heat cramps, *Medicine*, 1935, xiv, 323-376

100° F Working temperatures in various industries are often extraordinarily high 112° to 135° F in sugar refineries (Coplin), 125° F in the stoke-hole of a warship (Phelps), 150° F in a pullman diner kitchen (Clendening) Even higher temperatures are encountered by certain workers in the steel industry

Contrary to the general impression, the relative humidity of the working atmosphere was not found to be an important factor in the production of heat cramps

Talbott does not discuss in detail the relationship of the character of the muscular work to the incidence of heat cramps It is apparent from its industrial distribution that it is far more common among those doing heavy physical labor There is some evidence also that the cramps are most apt to affect the muscles which have been most actively employed The observation of cramps in pullman cooks indicates, however, that heavy muscular exertion is not an absolute essential It is certainly, nevertheless, a more vital factor in the production of heat cramps than it is in the development of either heat stroke or heat prostration

Defective general hygiene, ill health, inadequate assimilation of food, acute alcoholism and a recent attack of cramps were all found, from an analysis of the series of cases observed by Talbott in the Youngstown area, to be predisposing factors

An important observation which has been made by a number of students of this condition is that the incidence of heat cramps is greatest during the first few days of a hot wave and that there is a decreasing susceptibility as the hot weather continues This plainly suggests the presence of a process of adaptation of the body to continued environmental heat From certain data available it seems probable that the mechanism of this adaptation may involve the amount and the composition of the sweat secreted The observations of Moss* suggest that acclimatization to heat may involve a doubling of the sweat output, while those of Dill† indicate that adaptation includes the secretion of sweat containing a much reduced percentage of chlorides The results of these studies are at present more suggestive than conclusive

It is a point of definite value that the incidence of heat prostration is said to be greatest after the heat wave has continued for some time, since this difference from the time of highest incidence of heat cramps is strongly in favor of a fundamental difference in the pathogenesis of the two conditions Further statistical data to soundly found this distinction would be desirable

Talbott has made careful metabolic studies of 32 cases of heat cramps from the mills of the Youngstown area Very marked changes in concentration of many of the constituents of the blood and urine were found,

* Moss, K N Some effects of high air temperatures and muscular exertion upon colliers, *Proc Roy Soc London, Series B*, 1923-24, xcv, 181

† DILL D B, JONES, B F, EDWARDS, H T, and OBERG, S A Salt economy in extreme dry heat, *Jr Biol Chem*, 1933, c, 755

and as a result of these observations our knowledge of the condition has been notably advanced

The findings in the arterial blood indicated a marked anhydremia. Serum protein was greatly increased on admission—in one instance to 10.6 grams per cent. The increase was found due to the globulin fraction. The serum protein fell toward normal levels during the first days in the hospital but this decrease was not strictly parallel to the improvement in the clinical condition. The concentration of the hemoglobin, as measured by the oxygen capacity, was increased in correspondence to the serum protein increase. The rise in number of red cells paralleled closely the increase in hemoglobin. The anhydremia did not consist only of serum water loss since there was also a loss of 1 to 5 per cent from the red cells. The extent of the concentration of serum protein and hemoglobin was comparable to that found in severe cholera. Blood volume determinations were not made, and data on the specific gravity of the blood are not given.

It is interesting that in spite of these evidences of severe dehydration the amount of urine voided on the day of admission to the hospital was surprisingly large, varying between 400 and 800 c c.

The concentration of electrolytes in the serum of patients with cramps was found altered even in the mild cases. The serum chloride and the serum sodium were consistently diminished. The concentration of serum chlorides on admission was only twice found above 100 m eq and in one case it was 79.8 m eq. The minimum serum sodium concentration was 121.0 m eq and the maximum was 140.0 m eq. The urine in most instances showed a relative absence of sodium and chloride and in severe cases this persisted for several days. During the first few days in hospital balance studies showed a marked retention of sodium, chloride and water with a resultant gain in weight which averaged 4.4 pounds. These findings confirmed and greatly extended earlier observations by Edsall, Raschewskaja and others.

Serum sodium was the only inorganic base whose concentration was decreased in patients suffering from cramps. The concentration of potassium in the serum was normal or increased 1 to 3 m eq, and there was likewise in many patients a distinct increase in calcium concentration. A maximum of 14.3 mg per 100 c c of calcium was observed in two patients. On theoretical grounds the increase of calcium was considered greater than could be accounted for by the calcium binding power of the increased protein.

The variations in the arterial pH's covered a wide range but in most patients the reading was below 7.40, the apparent acidosis being explainable through loss of base. The pH of the urine on admission was usually about 5.0, a degree of acidity greater than was accounted for by the titratable acid found.

There was also noted an unexplained increase in the serum of inorganic

phosphates The non-protein nitrogen was elevated 10 to 25 mg per 100 c c above normal levels Blood sugars were within the normal range

An observation of great interest and possibly of importance was that in 14 of the 32 patients on admission the degree of oxygen saturation of the arterial blood was below 94 per cent and in one patient it was found to be 84.6 per cent

Talbott's analysis of these data has led him to feel that the decrease of serum sodium and serum chloride bears the most constant and significant relationship to the occurrence and severity of the cramps He feels that in each working subject a critical level exists for sodium and chloride, below which muscular cramps occur The loss of serum sodium and chloride is presumably through excessive sweating

The hypothesis is greatly strengthened by the striking therapeutic effects of the administration of sodium chloride as normal salt solution intravenously In severe cases 600 to 1,000 c c of the saline solution were administered, and in all instances the cramps were relieved before the infusion was terminated and could not be brought back thereafter by artificial means In less severe cases the ingestion hourly of a 1 gram salt tablet was effective In the prevention of cramps the value of an increased salt intake has been claimed by a number of observers It has been dispensed to workers in the form of salt tablets but recent opinion favors its introduction into the drinking water to produce a 0.1 per cent concentration Such a solution is without perceptible saline taste

The argument in favor of a specific relationship of lowered serum sodium and chloride to heat cramps would be further strengthened if data from the control series of heat prostration cases had been furnished showing the absence of any similar changes in the serum of these patients

These studies mark a definite advance in our knowledge of this interesting condition It is apparent that the entire mechanism of heat cramps is not yet clear and that many of the actual findings are unexplained, but definite data concerning one fundamental feature of this mechanism have been obtained In how far this knowledge will yield insight into the nature of other varieties of muscle cramps future research will show

REVIEWS

The Practitioner's Library of Medicine and Surgery Supervising Editor, GEORGE BLUMER, M A (Yale), M D, F A C P, David P Smith Clinical Professor of Medicine, Yale University School of Medicine, Consulting Physician to the New Haven Hospital *Volume X Dermatology and Syphilology* Associate Editor C GUY LANE, M D, Instructor in Dermatology and Syphilology, Harvard Medical School lxviii + 1043 pages, 286 illustrations D Appleton-Century Company, Inc, New York 1936 Price, \$10 00 a volume

The tenth volume, Dermatology and Syphilology of The Practitioner's Library of Medicine and Surgery, is a very well planned addition to this series, the preceding volumes of which have been noticed from time to time in the ANNALS This book profits by the advantage derived from having a limited number of contributors, for the monographic treatment of a relatively large field promotes balance and thoroughness Thus we find, among the larger divisions of the volume, General Considerations, by C Guy Lane, constituting a chapter of 99 pages, covering all of the fundamental considerations of histology, physiology, basic lesions, diagnostic methods and general therapy The second chapter dealing with Infections of the Skin, by Frederick D Weidman, requires 200 pages and is admirably done in the concise, illuminating style of which he is a master Again, the chapter on Syphilis, by J E Moore, is 189 pages in length Thus this volume is in fact a group of treatises upon major divisions of dermatology and syphilology by experts in those particular fields

As with other volumes of this series the technical book-making is excellent, and the errors over which reviewers are prone to gloat, extremely few Perfection has, of course, not been attained For instance, Figure 8 on page 843 appears in the list of figures as a chancre of the lip, although the legend accompanying the figure states that a chancre is precisely what the lesion depicted is *not* Seldom have large volumes, such as the members of this series, appeared with as few typographical errors as these have shown

In general, this volume is fully in harmony with the modern trend which relates Dermatology intimately to the practice of Internal Medicine Skin diseases are no longer to be considered as isolated external phenomena, known by purely descriptive terms, but rather as the superficial manifestations of disease states affecting the entire body economy The needs of the general practitioner have been kept in mind, the growing importance of occupational diseases of the skin recognized, and a thoroughly practical discussion of syphilis provided The liberal use of illustrations and the very complete index add to the value of this book as a reference work in the recognition and treatment of the skin conditions which so often come to the attention of the general practitioner

C V W

Lactobacillus Acidophilus and Its Therapeutic Application By LEO F RETTGER, MAURICE N LEVY, LOUIS WEINSTEIN and JAMES E WEISS 203 pages, 14 X 21 cm Yale University Press, New Haven, Conn 1935 Price, \$2 50

This volume represents an interesting study of a phase of therapeutics not commonly used by the average physician The authors establish the bacteriological properties of the acidophilus group of organisms and draw attention to the inaccurate nomenclature employed by certain investigators This is particularly true concerning the oral and dental types of lactobacilli which have been confused with *B acidophilus*

The authors stress the fact that acidophilus milk is not a cure-all However, it is useful in instances in which the complaint is directly referable to the gastro-

intestinal tract and especially in cases of simple chronic constipation as well as in many other types of constipation. They believe that other laxatives interfere with the effectiveness of the acidophilus treatment and therefore should be omitted. However, the importance of the oral administration of dextrin and lactose in prolonging the activity of an acidophilus implantation is stressed.

A routine plan of administering *B. acidophilus* in the form of milk is outlined. Even under such conditions implantations were obtained only in certain groups of cases and then often only after several courses of treatment. Of the patients who responded favorably a large percentage became so-called "implanters." Satisfactory results were obtained in many cases of "mucous colitis" or "irritable colon" and in a number of cases of diarrhea associated with ulcerative colitis.

Although these investigations seem promising one has the feeling as one reads the book that inasmuch as the acidophilus group of organisms are short-lived and require constant feeding in order to maintain the acidophilus implantation it is doubtful whether one can hope to obtain a continuous therapeutic effect even in those cases in which implantation has apparently taken place for a period of weeks. Moreover, the authors have observed that continual replenishment of the acidophilus strain by ingestion of acidophilus milk is necessary in the great majority of patients.

S M

The Extra-Ocular Muscles. By LUTHER C. PETER, M.D. 351 pages, 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1936. Price, \$4.50.

This second edition of Dr. Peter's book contains 351 pages with 136 engravings and five colored plates. It is divided into six parts as follows: Part I, Anatomy and Physiology; Part II, Heterophoria; Part III, Heterotropia or Concomitant Squint; Part IV, Paralytic Squint; Part V, Surgical Technique; and Part VI, Nystagmus or Talantropia.

In Part I the anatomical illustrations and descriptions are largely from Whitnall's "Anatomy of the Human Orbit" and are most excellent. That portion which deals with the physiology of the muscles is clearly written and illustrated. Parts II and III devoted to the non-paralytic phorias and tropias are sufficiently clear so that not only the specialist but the internist as well will be able to classify these defects. Part IV which deals with the diplopias and paralytic squints is very clear and explicit. By referring to plates 4 and 5 one should theoretically at least be able to diagnose any type of muscle palsy. Unfortunately, however, most cases are so complicated that even the authorities are often unable to determine just what muscle or group of muscles is involved. In Part V the author describes the surgery of the ocular muscles and outlines the technic of those operations which have been most successful in his hands. In many instances the methods are original while in others they are modifications of previously described operations.

The reviewer regrets that the author did not include the surgery of ptosis as well since this is due to abnormalities of the levator palpebrarum which he describes in the anatomical section.

The publishers as well as the author should be commended for this second edition which brings the subject up to date and thereby fills a want not only for the internist but more especially for the ophthalmologist.

C A C

Treatment in General Practice (Articles republished from the British Medical Journal) 260 pages, 15 × 22 cm. Paul B. Hoeber, Inc., New York. 1936. Price, \$3.50.

The book consists of a number of short articles of variable value on the treatment of certain diseases of the respiratory and cardiovascular systems as well as of certain specific fevers. The editorial policy has been to insist on clarity "to the

point of dogmatism" and there is no doubt but what this objective has been attained. In the section on diseases of the respiratory tract there are many points in symptomatic therapy which physicians in this country will find interesting and valuable, but in general there is little which has not long been included in general practice. A few recommendations are made which are astonishing. "When the patient (with pneumonia) is seen within the first three days a vaccine or a serum should be given. A vaccine has the great advantage that it can be carried in the bag and is immediately available." Under the treatment of asthma by desensitization it is said that "it is better to employ a solution of the four common irritants as one or more of them will be specific for the case, while the others will have a non-specific effect." For technic and dosage the reader is referred to the manufacturer of this solution.

The section on the treatment of certain contagious diseases well repays careful reading though in the article on septicemia the attitude of the writer seems decidedly uncritical.

There is also a great deal of value to certain of the articles on treatment of cardiovascular diseases. In summary, however, the chief interest of the book to the American readers will lie in the opportunity it affords to compare the routine of practice in this country with that in England.

M C P

Prescription Writing and Formulary The Art of Prescribing By CHARLES SOLOMON, M D, Assistant Clinical Professor of Medicine, Long Island College of Medicine, with a foreword by Lewellys F Barker, M D. 351 pages, 16 X 23.5 cm. J P Lippincott Co, Philadelphia. 1935.

In the writing of this book, Dr Solomon proposed to bring before the reader the use of drugs in the treatment of disease providing a sound and scientific basis for prescription writing. The book is divided into three parts. Part I is of an introductory nature containing the history of prescription writing from ancient through medieval and modern times. Also there are many practical suggestions to the young physician, such as the prescribing of official remedies rather than proprietary medicines of a more expensive nature. Interesting comments are made on the relationship of the physician and the pharmacist and also on the character and relative usefulness of drugs which are carried in the doctor's handbag. In this section also the absorption and excretion of drugs are discussed in addition to the various avenues of administration. Part II deals with such practical subjects involved in prescription writing as the preparations of solutions, metrology, the use of English and Latin in prescriptions, incompatibilities, construction of the prescription, posology and suggestions for prescription writing. Part III is somewhat separate from the other part of the volume and deals with a number of prescriptions and formulas used in the treatment of the various diseases of the systems of the body. Thus, under drugs having local action, the demulcents and emollients are set forth in typical prescriptions. Under drugs acting on the gastrointestinal tract, the stomachics, antacids and cholagogues are mentioned. In addition there is included a group of biological products illustrating the use of the various serums, vaccines, and antitoxins.

On the whole this volume by Dr Solomon is well written and excellently organized and will serve a very timely need if it reaches the hands of the young practicing physician. Although essentially a book of practical therapeutics its pharmacological foundations are sound. Dr Solomon adheres to the modern principle of simplicity in prescribing and in practically all of the formulas and typical prescriptions included in the book a marked departure from the typical polypharmaceutical prescriptions is noted.

On the whole the author fulfills his purpose in writing this volume and in the reviewer's mind it deserves careful consideration among those physicians who still believe that drugs are an important part of the physician's armamentarium.

J C K, JR

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the following gifts received recently for the Library of the American College of Physicians from the authors

- Dr John Favill (Fellow), Chicago, Ill—1 book, "The Relationship of Eye Muscles to Semicircular Canal Currents in Rotationally Induced Nystagmus",
Dr Samuel Weiss (Fellow), New York, N Y—1 book, "Diseases of the Liver, Gall Bladder, Ducts and Pancreas", 1 bound set, "Clinical Lectures on Gastroenterology," and four reprints,
Dr C Frank Brown (Fellow), Dallas, Tex—2 reprints,
Dr David N Kremer (Fellow), Philadelphia, Pa—2 reprints,
Major James Stevens Simmons (Fellow), M C, U S Army—1 reprint,
Dr William C Cooke (Associate), San Diego, Calif—2 reprints,
Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint
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PUERTO RICO MEETING OF MEMBERS OF THE COLLEGE

The first formal meeting of the members of the American College of Physicians residing in Puerto Rico was held May 26, 1936, with Dr Ramon Suarez, Governor, presiding

Dr Juan Pons, Dr Harry P Colmore, Dr Antonio Ortiz, Dr O Costa Mandry, R R Rodriguez Molina, Dr Guillermo S Marques and Dr Munoz McCormick were in attendance

Dr Suarez, as Governor, was appointed to act as president of the local chapter, and Dr O Costa Mandry was appointed secretary. It was decided to hold a meeting with a medical program once every two months. The next meeting will be held at the University Hospital, and will consist of clinical conferences and the presentation of cases

Dr W McKim Marriott (Fellow), for several years Dean and Professor of Pediatrics at Washington University School of Medicine, St Louis, has been appointed Dean and Professor of Research Medicine at the University of California Medical School, San Francisco

Major James Stevens Simmons (Fellow) of the Army Medical Research Board, Ancon, C Z, was elected president of the Medical Association of the Isthmian Canal Zone, at a meeting of this organization on June 16, 1936

Dr Ellen C Potter (Fellow), Director of Medicine, Department of Institutions and Agencies of the State of New Jersey, was the recipient of the honorary degree of Doctor of Laws at the commencement of Rutgers University on June 6

Dr Bernard Langdon Wyatt (Fellow), Tucson, Ariz, was unanimously voted the James M Stacey Award for 1936 by the Faculty Council of the College of Medi-

cine, University of Cincinnati, on June 6 The Stacey Award consists of a medal and an honorarium of \$100 00, and is given for significant contribution in the field of focal infection

Dr Samuel E Munson (Fellow), Springfield, Ill, presented a paper on "The Clinical Aspects of Amebiasis" before the annual meeting of the Illinois State Medical Society at Springfield, in connection with a symposium on "Amebiasis," presenting all the phases of the Chicago epidemic of 1933

Dr Hugh B Campbell (Fellow), Norwich, Conn, has been elected vice-president of the Connecticut State Medical Society for the coming year

Major Raymond O Dart (Fellow) of the Army Medical Museum, Washington, addressed the Washington Ophthalmological Society recently on "Ocular Tumors"

Friends and students of Dr Anton J Carlson (Fellow), professor and chairman of the department of physiology, University of Chicago, presented to the University a bust of Dr Carlson, the unveiling ceremonies taking place June 1 Dr Carlson was born in Sweden He came to America in 1891 and studied at Leland Stanford University in California After two years of teaching and research at Stanford University and the Carnegie Institution, he became assistant professor of physiology on the staff of the University of Chicago, and in 1914 was advanced to a full professorship

Life membership in the State Society of Iowa Medical Women was conferred upon Dr Jeannette Dean Throckmorton (Fellow), recently

Dr John A Foley (Associate), heretofore associate professor of medicine, Boston University School of Medicine, has been named clinical professor of medicine in that institution

Dr Lawrason Brown (Fellow), Saranac Lake, N Y, was awarded the honorary degree of Doctor of Science at the annual commencement of the Medical College of Virginia, Richmond, on June 2

A testimonial dinner was recently tendered Dr Charles W Burr (Fellow), Philadelphia, by his friends on the occasion of the fiftieth anniversary of his graduation in medicine and his election to the presidency of the Medical Alumni Society of the University of Pennsylvania Dr Daniel J McCarthy (Fellow) was toastmaster

Dr James H Means (Fellow and president-elect) will be one of the lecturers on the program of the twentieth annual course of medical lectures and clinics presented by the University of Washington during the week of July 20

Dr John G FitzGerald (Fellow), Toronto, has resigned as dean of the Faculty of Medicine of the University of Toronto, in order to make a survey of methods of teaching preventive medicine sponsored by the Rockefeller Foundation. Dr FitzGerald, with Dr Charles Edward Smith of Stanford University School of Medicine assisting, will visit medical schools throughout the United States, Canada, the British Isles and European countries. After the completion of the survey, Dr FitzGerald will return to Toronto as director of the school of hygiene and of the Connaught Laboratories of the University there.

Dr Joseph M Hayman, Jr (Fellow), Cleveland, has been elected secretary of the American Society for Clinical Investigation.

Dr Chester M Jones (Fellow), Boston, and Dr Ernest H Gaither (Fellow), Baltimore, have been elected president and vice-president, respectively, of the American Gastro-Enterological Association.

Dr Henry C Sweany (Fellow), Chicago, will represent the United States in respect to the discussion of the biologic subject, "Radiological Aspects of the Pulmonary Hilum and Their Interpretation," at the tenth conference of the International Union against Tuberculosis, in Lisbon, Portugal, September 7 to 10.

Dr Fred H Kruse (Fellow) and Dr Harry C Shepardson (Fellow) have been made clinical professor of medicine and associate clinical professor of medicine, respectively, on the faculty of the University of California Medical School, San Francisco.

Dr Theodore G Klumpp (Associate), assistant clinical professor of medicine, Yale University School of Medicine, has been given a leave of absence for the academic year 1936 to 1937 to make a study of glandular and antianemic preparations with the Food and Drug Administration of the U S Department of Agriculture, Washington.

Dr Daniel L Finucane (Associate) has been appointed associate professor of clinical medicine at Georgetown University School of Medicine, Washington, D C.

Dr Coursen B Conklin (Fellow) has been reelected secretary of the Medical Society of the District of Columbia.

Under the presidency of Dr Louis H Fligman (Fellow), Helena, Mont, the Medical Association of Montana held its fifty-eighth annual meeting at Billings, Mont, July 8 to 9. Dr Ernest D Hitchcock (Fellow), Great Falls, and Dr Allen R Foss (Fellow), Missoula, delivered papers on "Highlights in Routine Gastric Examinations" and "Manifestations of Allergy in General Practice," respectively.

The Catawba Valley Medical Society met on May 26 at Morganton, N C, with the following guest speakers from the membership of this College

Dr John Russell Twiss (Fellow), New York City, "Differential Diagnosis and Clinical Management of Different Types of Gall-bladder Disease",

Dr Milton A Bridges (Fellow), New York City, "Dietary Management of Gall-bladder Disease",

Dr Isaac H Manning (Fellow), Chapel Hill, N C, "Hospital Saving Association of North Carolina"

Dr Samuel D Ingham (Fellow), Los Angeles, has been elected vice-president of the American Neurological Association

Under the presidency of Dr Julius H Hess (Fellow), the Chicago Medical Society held its annual banquet and the installation of new officers on June 17

Dr Ernest E Irons (Fellow) is retiring as dean of Rush Medical College to assume the title of professor of medicine Dr Irons will remain as chairman of the department of medicine Announcement has been made that the School of Medicine of the Division of Biological Sciences at the University of Chicago and Rush Medical College are now combined in one institution to be known as the Rush Medical College of the University of Chicago Undergraduate medical education will be continued at the west side school The medical schools are united in one departmental organization under the dean of the biological sciences Dr Emmet B Bay will act as associate dean on the west side It is said that the number of medical students will be greatly diminished during the next five years and graduate instruction will be introduced on an increasing scale, with the possibility that eventually graduate study may supersede undergraduate study entirely on the west side

Dr John Richards Aurelius (Fellow), St Paul, Minn, has been elected president of the Minnesota Radiological Society

Dr Thomas Hodge McGavack (Associate), San Francisco, has been appointed associate professor of medicine at the New York Medical College and Flower Hospital, beginning July 1

Dr William D Stroud (Fellow), Philadelphia, has been elected president of the Philadelphia Heart Association

Dr Joseph McFarland (Fellow), professor of pathology, University of Pennsylvania School of Medicine, retired June 30, having reached the age limit He will continue as professor of pathology in the Evans Dental Institute and the Veterinary School, both departments of the University of Pennsylvania

Dr Henry K Mohler (Fellow) has been promoted to associate professor of therapeutics at Jefferson Medical College, Philadelphia

Dr Guy W Wells (Fellow), Providence, R I, was elected secretary of the Rhode Island Medical Society at its annual meeting June 3

Dr Hugh S Cumming (Fellow), Washington, D C, is chairman of the Washington committee on arrangements for the Second National Conference on College Hygiene to be held in Washington, D C, December 28 to 31, under the joint sponsorship of the American Student Health Association, the National Health Council and the President's Committee of Fifty on College Hygiene It is announced that there will be no formal program with prepared addresses, but the work will be divided into five sections health service, health teaching, organization and correlation, special problems and relationship of college hygiene to teacher training and secondary education Dr Livingston Farrand, president of Cornell University, is chairman of the conference

Dr Ray M Balyeat (Fellow), Oklahoma City, Dr David J Davis (Fellow), Chicago, Dr Paul J Hanzlik (Fellow), San Francisco, Dr Russell L Cecil (Fellow), New York City, and Dr Cyrus C Sturgis (Fellow), Ann Arbor, are members of the College who appeared on the formal program of the fifteenth annual meeting of the Pacific Northwest Medical Association in Portland, Ore, July 8 to 11

Dr Virgil E Simpson (Fellow), Louisville, Ky, was guest speaker on May 19, 1936, at the meeting of the Southwestern Medical Society at Paducah Ky His subject was "The Physician, The Pharmacopoeia, Prescriptions and Philandering" Dr Simpson was also the guest speaker at the Harlan County Medical Society at Harlan, Ky, on May 30, 1936 Subject "The Social Security Act and the Medical Profession"

Dr Charles James Bloom (Fellow), Professor of Pediatrics, Post-Graduate School of Medicine, Tulane University of Louisiana, was one of the guest speakers of the State Medical Association of Texas before the Section on Medicine and Diseases of Children and the General Meeting, held in Houston, Texas, May 26, 27, 28, 1936

Dr Herbert T Kelly (Fellow), Philadelphia was guest speaker June 9, at the meeting of the Cumberland County (New Jersey) Medical Society The subject of his address was "Diabetes"

OBITUARIES

DR ALDEN H WILLIAMS

Dr Alden H Williams (Fellow), Grand Rapids, Mich , died June 10, 1936, of coronary occlusion, aged, 59 years

Dr Williams was born at South Gibson (Susquehanna County), Pennsylvania, and attended the Bloomsburg State Normal School He, however, became interested in medicine and entered the University of Michigan in 1894, receiving his medical degree in 1899 He did postgraduate work in Berlin, Germany, during 1907, and pursued several postgraduate courses, especially in radium and roentgen-ray therapy, in this country in later years During the World War he was in the Radiological Service of the U S Veterans Bureau He later became Chief of Staff of the Butterworth Hospital in Grand Rapids He was a past president of his county medical society, a member of the Michigan State Medical Association and a Fellow of the American Medical Association His interests were primarily in the field of radiology, and hence he was an active member and former president of the Radiological Society of North America, a member of the American Roentgen-Ray Society and other organizations in this field He became a Fellow of the American College of Physicians in 1922

DR ALANO E PIERCE

Dr Alano E Pierce (Fellow), Minot, N D , died March 14, 1936, of pneumonia, aged, 35 years

Dr Pierce was born at Dexter, Minnesota, April 22, 1900, he received the degree of Bachelor of Arts from the University of Minnesota in 1921, the degree of Bachelor of Science from the same institution, 1923, the degree of Bachelor of Medicine from the University of Minnesota Medical School in 1924, and his degree of Doctor of Medicine from the same institution in 1925 He did post-graduate study at the University of Vienna from February to November, 1926 He became Assistant in Medicine at the University of Minnesota Medical School in January, 1927 His internship was spent at the Minneapolis General Hospital He went to Minot, N D , in 1929, and became a member of the regular staff of the Trinity Hospital and became associated with the Northwest Clinic as Internist

He was a member of the Northwest District Medical Society, the North Dakota Medical Society and a Fellow of the American Medical Association He became a Fellow of the American College of Physicians on March 22, 1931

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THE PRESENT STATUS OF PERNICIOUS ANEMIA, EXPERIENCE WITH 600 CASES OVER EIGHT YEARS '

By CYRUS C STURGIS, F A C P, *Ann Arbor, Michigan*

INTRODUCTION

It is not the purpose of this article to present new and detailed data concerning pernicious anemia, but merely to give a number of conclusions dealing with some aspects of the etiology, diagnosis, prognosis and treatment of the disease which are based upon an experience with over 600 patients whom we have observed during the past eight years. The remarkable development of our knowledge of this condition during the last decade constitutes one of the most brilliant chapters in the history of medicine, for not only has a means been found of controlling a condition which had hitherto been considered fatal, but new fundamental facts of importance bearing on the physiology and pathology of many other blood diseases have been brought to light.

It has been firmly established, mainly through the investigations of W B Castle and his collaborators, that the cause of the anemia is a lack, or diminished amount, of an unidentified, enzyme-like substance, which is secreted by the mucosa of the stomach. This has been called the intrinsic factor which functions normally to control the rate of red blood cell production in the bone marrow. When there is a decreased amount or absence of this substance, the rate of blood production is diminished and an anemia results. Almost all students of the disease agree that the work of Castle is sound and has solved, at least in part, the problem of the etiology of the disease. His work has opened up an entirely new relationship between the gastrointestinal tract and blood formation which points the way to many new experimental approaches of studying blood diseases.

A detailed discussion concerning the diagnosis of pernicious anemia is not within the province of this paper, but several important diagnostic points should be emphasized which have arisen from a study of this group of patients. In the first place, not one single patient of this group has had free

* Presented at the Detroit meeting of the American College of Physicians, March 4, 1936

hydrochloric acid present in the gastric secretion, even following stimulation with histamine. Many thousand gastric analyses have been reported in the literature and in only an occasional case has "free" hydrochloric acid been reported. An achlorhydria, therefore, is essential to the diagnosis of true Addisonian anemia, and the presence of this acid in the gastric secretion practically eliminates it from consideration as a diagnostic possibility. It is impossible to say why several cases, of many, have been reported as having free acid, but two possibilities can be suggested: (1) that the patient did not have true pernicious anemia but some other type of macrocytic anemia (such as cirrhosis of the liver), and (2) that for some unknown reason free hydrochloric acid is actually present in the gastric secretions of an occasional patient with true pernicious anemia. Concerning the gastric secretions it can also be stated that in our experience free hydrochloric acid never returns when the patient has a complete hematopoietic remission although the gastric complaints almost always subside at this time. From a diagnostic standpoint it should also be emphasized that, in addition to the usual symptoms of any anemia, such as weakness, pallor, dyspnea and palpitation, there is another symptom which should almost always be present before the diagnosis of pernicious anemia can be made, and this is numbness and tingling of the hands and feet. This may be the initial symptom of the disease, but if not, it occurs at some time during its course in 90 per cent of the patients. If this complaint is lacking, it arouses a strong suspicion that the patient is suffering from some other variety of anemia than the pernicious type. Recurrent glossitis is also a symptom which has long been recognized as occurring in pernicious anemia but it has not been appreciated that it occurs in fully two-thirds of the patients. It likewise may be an inaugural symptom and precede the anemia by several years.

Brief reference only will be made to the changes in the blood. A careful study of our patients has confirmed the opinion of others that the most typical morphological change in the peripheral blood, at all stages of the anemia, is the presence of large oval red blood cells, or, as is said, a macrocytosis is present. This is more striking when the anemia is pronounced but it is also the last remaining evidence of abnormality as the blood reaches approximately normal limits. The predominance of small, rather than large cells, is almost conclusive evidence against an anemia of the pernicious type.

A sufficient period has now elapsed to permit a statement concerning the efficacy of various types of treatment. The different therapeutic agents which have been used are raw or cooked liver, liver extract and Ventriculin and liver and stomach combinations for oral use, and liver extract for intramuscular or intravenous injections. From our experience, it can be said that any one of these forms of treatment can usually control the anemia of pernicious anemia if sufficient quantities are given. It is our opinion, however, after giving thousands of treatments over a period of several years, that the ideal form of therapy is the intramuscular injection of liver extract. It has the following advantages

1 Gram per gram of liver, it is many times more effective when given parenterally than it is by mouth. It has also been observed that the oral treatment may increase the red blood cell count in some patients to a maximum level of slightly less than 4 million per cu mm, despite the administration of huge doses.

2 Local or general reactions have not been observed following its use. When liver extract is given intravenously it is highly effective, but following about 10 per cent of the injections there is a disagreeable reaction characterized by a chill, fever, and often nausea and vomiting. This type of reaction is not seen following intramuscular injections. In a very few instances the intramuscular injection has been followed by allergic manifestations such as urticaria. This has usually occurred, however, when the patient has previously been treated with intravenous liver extract which probably sensitized him to the product. This state of sensitivity was apparently transient for after a relatively brief interval it was possible to resume the intramuscular injections without the production of allergic signs. This is not a matter of great importance because it occurs only rarely and probably can be avoided if intravenous liver extracts are not given prior to the intramuscular type of medication.

3 Another advantage is that the intramuscular injection eliminates all problems of utilization of the product through incomplete absorption from the gastrointestinal tract and also that of inadequate storage in the body. For example, one patient whom we treated had a macrocytic anemia which probably resulted from a surgical procedure which anastomosed the jejunum to the transverse colon. This created a condition whereby a sufficient amount of the blood regulating substance was not absorbed from the gastrointestinal tract. Large amounts of liver extract and Venticulin by mouth were without effect in this patient, whereas the blood returned promptly to normal when liver extract was given intramuscularly. Also a macrocytic anemia may develop through the inability of the liver to store and properly metabolize the blood regulating substance. This probably occurs when the liver, which is the main storage depot in the body for the blood regulating substance, is extensively damaged, such as it may be in cirrhosis. Intramuscular liver extract is efficacious under these circumstances when oral medication is less effective.

4 The treatment by intramuscular injections is regarded by most of our patients as the most convenient form of therapy as the blood may be maintained at a normal level by one injection weekly and ordinarily no other medication is required.

The only objections to the intramuscular treatment are (1) Individuals who live in isolated communities find it inconvenient or impossible to visit the physician at regular intervals for the injections. An attempt has been made, with only partial success, to instruct patients in the method of administering their own injections. (2) The expense of treatment may be greater, or less, than that with oral types of medication but this depends

largely on the charge which the physician makes for giving an intramuscular injection

What should be the ideal dosage of intramuscular liver extract? This is a difficult question to answer precisely, for the following two reasons (1) Pernicious anemia may be regarded as a disease with a deficiency which is probably relative rather than absolute. It is logical, therefore, to consider that some patients will require a greater dosage than others. (2) The concentration of liver extracts which are commercially available varies widely in the amount of active principle. For example, one manufacturer states that 1 c c is derived from 100 c c of liver, whereas another states that 2 c c are derived from 10 grams of liver.

For these reasons our advice to physicians in answer to this question is as follows. Give a variety of liver extract which is (1) clinically tested, (2) use the dose advised by the manufacturer, (3) control the dosage by making frequent red blood cell counts.

The latter statement should be strongly emphasized, for the level of the red blood cells is the best single criterion concerning the effectiveness of the treatment and it should be determined systematically and periodically in every patient with pernicious anemia who is being treated. A sufficient quantity of the material should be given to keep the red blood cells at a level between 4.5 and 5.0 millions per cubic millimeter. If a patient's blood has reached normal and for any reason the type of medication or the dosage is changed, then a red blood cell count should always be made at monthly intervals thereafter for several months to insure that adequate therapy is being administered.

The intramuscular preparation with which most of the patients of this series have been treated was standardized on the basis that 2 c c are derived from 10 grams of liver. The initial dosage of this preparation in a patient who has pernicious anemia should be 12 to 16 c c weekly in doses of 4 c c at a time, until the blood reaches normal. It is known that the red blood cell count with optimum treatment will increase at the rate of about 500,000 red blood cells per cu mm per week and, therefore, if the initial level of the red blood cells was 1 million per cu mm, it should reach normal in about 8 weeks. After the blood reaches normal, it has been observed that about 4 c c weekly, given at one dose, are required to maintain it at this level, although the limits of the maintenance dosage vary between 2 and 6 c c weekly.

Many times the question has been asked, "Is it possible to maintain the blood of a patient with pernicious anemia within normal limits indefinitely and the individual be kept in good health so that he can live out his normal span of life?" The answer is that he probably can, provided (1) Extensive cord lesions are not present when treatment is begun, (2) If an adequate amount of potent anti-pernicious anemic material is given, which requires the closest cooperation between physician and patient. A great majority of the present day failures in the treatment of pernicious anemia

are due to (1) The failure of the patient to appreciate that the therapy of pernicious anemia is merely one which controls the disease and does not eliminate its fundamental cause. It is necessary, therefore, that potent medication, in one form or another, be continued throughout the remainder of the patient's life, (2) The failure on the part of the physician to appreciate that the patient must remain under his observation, more or less continuously, for an indefinite period.

Perhaps the most important therapeutic problem in the field of pernicious anemia at present is the management of the spinal cord changes, and a great many opinions have been expressed concerning this. It is well recognized that the pathologic changes in the central nervous system, which occur as a complication in a fair proportion of patients with pernicious anemia, consist of actual degeneration of nerve fibers in the posterior and lateral columns of the cord which results in an ataxia with varying degrees of spastic paraplegia. As the process develops, there is a loss of control of the sphincter of the bladder with retention of urine, a resultant cystitis, and, if the condition progresses, an ascending pyelitis, with abscesses of the kidney, septicemia, bronchopneumonia and death. While anti-pernicious anemic therapy produces striking effects as far as the blood is concerned, the results attained in treating the central nervous system lesions are controversial. It has been our experience that there is often striking subjective improvement but that objective evidences of this occur in only a small per cent of the patients. On the other hand, patients have been observed who have made an unbelievable recovery. One woman of 61, with red blood cell count of 1,000,000 per cu mm, who was confined to bed with a well advanced combined degeneration of the cord, intense infection of the urinary tract, extensive decubitus ulcers, and incontinence of urine and feces, is now able to walk unassisted and does all of her own housework including the family washing. This improvement has been maintained over a period of four years.

The question has been asked, whether if a patient with pernicious anemia who has no evidence of cord changes is treated in such a manner that the blood is maintained at a high normal for an indefinite period, are cord changes likely to develop. The opinion of most observers is that this is unlikely, although it must be admitted that this question must remain unanswered until sufficient time has elapsed to give the facts for a statement which is based on actual observation over a long period of years. In our group of patients this has not occurred in a single patient during a period of eight years.

The present treatment of the cord changes, in addition to the management of the urinary infection and decubitus ulcers which may be present, is not complicated. It consists (1) in administering treatment which will cause the blood to return to a high level of normal and maintaining it there indefinitely. (2) Physiotherapy, which consists mainly in active motion produced by the patient's attempts to walk when supported by attendants,

(3) Reeducation in coordination of the muscles of the legs, and teaching the patient to use his eyes in guiding his walking attempts, as the sense of motion and position of his legs is, of course, usually destroyed by the lesions in the posterior columns of the cord

In addition to anti-pernicious anemia therapy, there are several minor therapeutic adjuncts which have been used by some physicians in treating pernicious anemia, although their value has not been definitely established. For example, should or should not dilute hydrochloric acid be given along with the liver therapy? It is true that all of these patients have an achlorhydria and in our experience the ability to secrete acid never returns when the blood reaches normal. In most instances, all gastrointestinal complaints disappear at this time but in a few patients they persist. In those in whom they do persist, dilute hydrochloric acid has been given and many times the complaints have disappeared. There are several possible explanations of this, as follows: (1) They might have disappeared without the hydrochloric acid therapy, (2) The psychic effect of giving the acid may have played an important rôle, (3) The hydrochloric acid might have had a truly beneficial effect.

In those patients with pernicious anemia in whom the gastrointestinal symptoms persist after the blood returns to normal, two possibilities should be considered: (1) the patient should be carefully studied to be sure a complicating gall-bladder condition is not present and this is not uncommon in patients with pernicious anemia, (2) dilute hydrochloric acid therapy may be given a therapeutic trial as it can do no harm and it might do some good.

Iron has been recommended by some as a beneficial drug in this disease. It certainly has no specific effect, but its use should be considered where certain conditions prevail, as follows: (1) When liver or stomach treatment is given, the red blood cell count always increases more rapidly than does the hemoglobin, as a result the color index always falls below 1.0. If this persists for a period of weeks, iron therapy, in the form of Reduced Iron, 0.5 gm t.i.d., is indicated. (2) A few patients have been observed who have had their condition complicated by chronic bleeding, usually from hemorrhoids. Then, of course, iron in the above dosage is clearly indicated.

Special diets and the addition of concentrated vitamins are rarely required in the treatment of pernicious anemia because the patient's appetite is so stimulated by the anti-anemic therapy that a large amount and variety of food are demanded. Occasionally a patient has been observed who apparently had a combination of pernicious anemia and a nutritional anemia. The diet under these circumstances is usually so obviously unbalanced that it is at once apparent and it is easily corrected by giving an ordinary diet.

The Prognosis This topic has been discussed briefly earlier in this article. Further information concerning this may be obtained by a consideration of the fatal cases in our series of 600 patients. During a period of one to eight years, slightly over 10 per cent of these patients died, and

approximately one-half of them succumbed to complications associated with lesions of the central nervous system. It is only fair to say, however, that almost all of this group either had advanced cord lesions when they were first observed, or that they failed to carry out the treatment as we had directed. Furthermore, many of these patients were treated before the parenteral method of administering liver was available. One can only speculate as to how many of them would have survived if they had been seen early in the course of the disease and if they had been intensively treated with intramuscular liver extract injections.

The remaining one-half of the fatal cases died of a variety of diseases which are not uncommon causes of death in this age group and the fatal conditions can only be regarded as having a coincidental association with pernicious anemia. The most common causes of death in this group were cardiac disease, hypertension and apoplexy, operations and accidents, pneumonia and malignancy. It is interesting to note that apparently none of these patients died of anemia per se, as their red blood cell counts were not reduced to a seriously low level when they were last observed.

In conclusion it may be said that pernicious anemia can no longer be looked upon as a disease which is necessarily fatal provided appropriate treatment can be applied, and, furthermore, in the near future there will undoubtedly be greater improvement and refinement of our present day methods of treatment.

VASCULAR PHYSIOLOGY AND CLINICAL MEDICINE

By EUGENE M. LANDIS, F A C P, *Philadelphia, Pennsylvania*

WHEN William Harvey first described the circulation of the blood over 300 years ago his observations were necessarily limited to the grossly visible portions of the circulatory system,—to the heart, arteries and veins. His evidence for a completely closed circulation, even on this basis, was so conclusive that the capillary portion of that circulation could be taken practically for granted. It was, in fact, 50 years before the capillaries themselves were observed under the microscope.

It seems as if investigation of capillary physiology has never been able quite to overcome this initial handicap of half a century. The heart and larger vessels received the painstaking attention of those interested in circulation, while the more minute parts of the vascular tree were, relatively speaking, neglected. This seems surprising because, from the functional standpoint, the heart, arteries and veins are subsidiary to the capillaries which have correctly been called "the workshop of the body."

Our present knowledge concerning this "workshop of the body" is the outcome of mutual stimulation and aid in the fields of clinical medicine and vascular physiology. For instance, the occurrence of edema, an outstanding clinical problem even before the time of Galen, stimulated earlier physiologists to ponder on the mechanism which controls the transportation and distribution of fluids throughout the body. In the normal individual the volume of tissue fluid suffers only transitory and relatively small changes despite wide variations in water intake. In patients with a tendency toward edema formation, on the contrary, the copious ingestion of water usually increases the normally meager amount of tissue fluid until clinical edema appears. They suffer apparently from a more or less serious breakdown of the normal mechanism of fluid transport.

The first reasonably complete hypothesis explaining the maintenance of equilibrium between blood and tissue fluid under diverse conditions was advanced by Starling,¹ a physiologist, in 1896 and was later expanded to explain tentatively the pathogenesis of edema. Starling called attention to the fact that those substances (such as salts, urea, creatinine, etc.) which pass easily through the capillary wall and are present in approximately equal concentrations in blood plasma and tissue fluid, cannot exert an osmotic pressure across the capillary wall and should not, therefore, affect the distribution of fluid except very temporarily. The plasma proteins, however, by reason of their greater molecular dimensions, are retained more or less efficiently by the capillary wall and can develop an osmotic pressure, amounting in man to approximately 26 mm. of Hg. This colloid osmotic pressure

* Read at the Detroit meeting of the American College of Physicians, March 5, 1936.
From the Department of Medicine, University of Pennsylvania.

of the blood, if unopposed, would filter fluid into the capillary blood from the tissue spaces. If this is true the relative constancy of blood volume and tissue fluid volume must depend primarily upon the balance between capillary blood pressure and the colloid osmotic pressure of the blood. This ingenious concept, though theoretically sound, was still open to criticism owing to the difficulties surrounding the measurement of capillary blood pressure.

In 1917 Epstein,² a clinician, emphasized the importance of hypoproteinemia in the pathogenesis of nephrotic edema. According to Starling's view this type of edema could be explained logically by the general lowering of colloid osmotic pressure which, in association with a normal capillary blood pressure, would favor filtration of fluid and, at the same time, hinder absorption from the tissue spaces.

War edema, associated with protein starvation, was also found during this period to be accompanied by hypoproteinemia, the edema disappearing when the plasma protein percentage rose to normal. Further clinical study by Krogh,³ Schade,⁴ Govaerts,⁵ Meyer⁶ and others verified the importance of hypoproteinemia in some types of edema, but showed that in other types the plasma protein percentage was usually within normal limits. The general problem of normal fluid balance and the clinical problem of edema then seemed too complex to be explained by simple physical principles.

Until rather recently the capillaries were generally believed to be inert, thin-walled tubes serving to conduct blood through the tissues in whatever quantity the arterioles might supply. About 1920 the work of Krogh,³ a physiologist, and of Lewis,⁷ a clinician, supplied from two directions impressive evidence showing that the capillary vessels are independently contractile and that they are capable of responding individually in a delicate manner to the circulatory needs of the immediately adjacent tissues. Even so the great transporting medium, the blood stream, is still separated from almost all the tissues it serves by a single layer of endothelial cells which form the walls of the capillary vessels. Obviously the interchange of substances between blood and tissues must depend fundamentally upon the properties of this membrane in association with the physical forces controlling the flow of blood past the membrane.

The primary factors involved in a quantitative study of the movement of fluid through a membrane are (a) the total area of filtering surface available, (b) the properties, particularly the permeability, of the membrane itself, and (c) the pressures exerted on the fluid both inside and outside the membrane.

The collective area of capillary wall available for fluid interchange is relatively enormous. Krogh³ estimated that the total surface of capillary wall in the body of an average-sized man must exceed 6,300 sq meters or 68,000 sq feet. In other words the total collective area of capillary endothelium in the adult human body can be visualized as a microscopically thin membrane three feet wide and over four miles long. In the capillary net-

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work one cubic centimeter of blood is exposed to a filtering surface of 7,300 sq centimeters or over 7 sq feet. Obviously very rapid interchanges are favored by areas of this magnitude.

In the second place, rapid interchange of water and dissolved salts is aided by the inherent properties of the capillary endothelium which is far more permeable than other living membranes so far studied quantitatively. Under comparable conditions⁸ water would pass through the frog's capillary wall three thousand times more rapidly than through the surface membrane of a typical cell and over one hundred times more rapidly than through the membrane of the human erythrocyte.

The significance of this extensive filtering area combined with great permeability can be expressed by a calculation which is admittedly approximate but illustrates the order of magnitude of possible effects. Assuming that the capillary wall of man is as permeable as the frog's capillary wall, the total plasma volume of a man could be filtered through his calculated 68,000 sq feet of endothelium within 10 seconds at a capillary pressure of only 10 mm of Hg if there were no force retaining fluids within the blood capillaries. Normally the activity of the vasomotor system prevents the entire peripheral vascular bed from opening simultaneously. In addition, the plasma proteins, by their colloid osmotic pressure, limit the loss of fluid from the blood stream. Only in widespread injury of the vascular endothelium would it be possible for fluid to leave the vascular system at such a deleteriously rapid rate.

Quantitative studies of the third factor, namely capillary blood pressure, offer some technical difficulty. Capillary blood pressure has been measured by many indirect methods, no one of which is entirely free from criticism. The estimates of pressure thus obtained by different observers ranged from far below to far above colloid osmotic pressure. Plethysmographic methods of determining the relation between capillary blood pressure and fluid movement require using masses of tissue containing large numbers of capillaries. The interpretation of these results is often difficult because of changing diameter, pressure and rate of flow in the separate vessels composing the capillary network. These variables can be reduced in number and more adequately controlled by studying single capillaries directly—thus limiting observations to what is, in fact, the smallest unit of the circulatory system.

To measure venous blood pressure directly it is necessary to use a needle small enough to be inserted easily into a vein, similarly, to measure capillary blood pressure directly the puncturing needle must be thinner than a single capillary. Chambers,⁹ an anatomist, had devised delicately adjustable micro-manipulators for the microscopic dissection of single cells. Using this technique and micro-pipettes measuring four to eight thousandths of a millimeter across at their tips it was possible, under the microscope, to pierce single capillaries at various locations.¹⁰ Capillary blood pressure could then be measured repeatedly for minutes, or with luck, for hours by determining

the pressure that must be exerted upon the fluid in the pipette to balance exactly the blood pressure in the capillary under observation

From a large number of single determinations in the main anatomical subdivisions of the vascular tree it became evident that average blood pressure in the arteriolar portion of the capillary network is measurably higher than that in the venous portion. Such a gradient of capillary blood pressure was observed in the four species studied (frog, rat, guinea pig and man) but the absolute level of pressure at which this gradient is maintained was found to differ considerably according to species. In the frog, for instance, arterial capillary pressure amounts to 14 cm water, venous capillary pressure to 10 cm water¹⁰. For man these figures are 45 and 22 cm respectively¹¹. If Starling's original hypothesis is correct the colloid osmotic pressure of human and amphibian plasma should show corresponding differences. In general this is the case since frog plasma has a colloid osmotic pressure between 7.5 and 13.0 cm water, human plasma about 36 cm water. The rat and guinea pig occupy an intermediate position in both respects¹². These findings are in accord with the concept that filtration favored in the arteriolar part of the capillary network will be balanced by absorption in the venous part of the capillary network.

Further development of micro-injection methods made it possible to measure the filtration and absorption of microscopically small volumes of fluid by single capillaries of the frog's mesentery¹³. It was then found that the rate and direction of fluid movement through the endothelium depended upon the relation between capillary blood pressure and the colloid osmotic pressure of the plasma,—supplying direct evidence that the capillary wall acts as a passive, though highly permeable, membrane. If capillary pressure is greater than the colloid osmotic pressure of the plasma, fluid is filtered into the tissue spaces. If capillary blood pressure is lower than the colloid osmotic pressure of the blood, fluid is absorbed from the tissue spaces. The rate of filtration or absorption is directly proportional to the difference between capillary blood pressure and the colloid osmotic pressure of the plasma. In the capillary network as a whole these two forces are normally approximately equal so that, on the average, filtration and absorption balance.

In human subjects the filtration produced by elevating capillary pressure can be demonstrated by enclosing the forearm in a plethysmograph specially constructed to determine changes in the volume of extravascular fluid, or in other words, the volume of edema fluid produced by venous congestion. Measured in this way the rate at which fluid filters into the tissue spaces is, above a certain minimal level, directly proportional to venous pressure¹⁴. Owing to the large area of endothelium and its high permeability to water and salts, changes in the volume of tissue fluid can occur with great rapidity. When venous pressure is raised to 80 mm of mercury the initial rate of filtration is 11 c.c. per 100 c.c. of forearm tissue per hour¹⁴. Studies of the blood revealed that 100 cubic centimeters of arterial blood can lose as much

as 20 cubic centimeters of fluid in passing through the capillary bed of the forearm during such high-grade venous congestion¹⁵

If this initial rate of filtration were to continue unchanged, edema would be produced in the normal subject within an hour. Fortunately the tissues resist, at least temporarily, the distortion which the accumulation of extravascular fluid produces as it forces the tissue elements apart¹⁴. This tissue pressure, since it partially neutralizes high capillary pressure, plays an important, though temporary, part in preventing the development of edema.

Excessive filtration of fluid may be produced also by reducing the colloid osmotic pressure of the blood. Plethysmographic studies on the forearms of normal human subjects indicated that *lowering* the colloid osmotic pressure of the blood favors the filtration of fluid into the tissues to the same degree quantitatively as *raising* venous pressure¹⁶. In animals, Leiter¹⁷ and others produced edema by lowering experimentally the plasma protein percentage, thus simulating the hypoproteinemic edema of nephrosis or malnutrition.

The preceding discussion has summarized physiological evidence that the normal capillary wall exhibits the properties of an inert (that is, non-secreting) membrane which is practically impermeable to the plasma proteins. Chemical studies by Loeb¹⁸ and others compared the concentrations of electrolytes in edema fluid and blood plasma without detecting any chemical evidence that the capillary wall in patients with edema behaved differently from celloidin membranes of similar permeability. Other studies¹⁵ of the protein in edema fluid of patients and in the capillary filtrate of normal subjects showed that these fluids contained in general less than 0.3 per cent protein, while the plasma from which the fluid filtered contained from 6 to 7 per cent protein. The normal capillary wall in resting tissues is about 95 per cent efficient in retaining the plasma proteins of the circulating blood. Muscular activity,¹⁹ anoxemia²⁰ and venous congestion¹⁵ reduce the efficiency of the endothelium in this respect.

Capillary injury of any type impairs or destroys this normal impermeability to protein. The gross systemic effects of widespread endothelial damage were recognized clinically even before war injuries directed the attention of physiologists and physicians to the shock syndrome and its relation to the capillary circulation. The local effects of vascular injury may be demonstrated and measured quantitatively, again by studying microscopically the ultimate functional unit of the circulatory system. Certain colloidal dyes perfused through single capillaries are retained by the normal endothelium. If the capillary is injured mechanically by light pressure with a microscopic glass rod the wall becomes highly permeable. The colloidal dye passes very rapidly through the injured endothelium though still retained by the adjacent normal endothelium²¹. After mechanical or chemical injury erythrocytes originally separated by plasma are concentrated and compressed into solid masses in the injured regions, indicating that plasma as a whole, including protein, filters rapidly through the damaged endo-

thelium In such capillaries the plasma proteins lose their power of retaining fluid since they pass easily through the injured wall and can exert no colloid osmotic pressure Fluid then filters into the tissue spaces approximately seven times more rapidly than normal and at capillary pressures which under normal conditions would bring about absorption¹³ In view of this seven-fold increase in permeability the rapidity with which shock or inflammatory edema develops does not seem so extraordinary

TABLE I

Factors Favoring Edema Formation	Clinical Examples
A Primary	
1 Elevated capillary pressure	1 (a) External pressure on veins (b) Thrombophlebitis (c) Cardiac edema with venous congestion
2 Lowered colloid osmotic pressure	2 (a) Nutritional edema (b) Nephrotic edema (c) Cardiac edema, late stages with malnutrition
3 Damage to capillary wall	3 (a) Inflammatory edema (b) Nephritic edema (c) Cardiac edema (?), chronic anoxemia
4 Lymphatic obstruction	4 (a) Lymphedema (b) Cardiac edema with venous congestion
B Contributory	
5 Low tissue pressure	5 Edema of periorbital tissues and genitalia
6 High salt intake	6 Increases edema if water is available
7 High fluid intake	7 Increases edema if salt is available
8 Warm environment	8 (a) Heat edema (b) Increases all types of edema
9 Disturbed innervation	9 (a) Tropho edema (b) Unilateral edema in hemiplegia

By combining available clinical and physiological data the factors concerned in the pathogenesis of edema may be summarized tentatively under two heads (table 1) Those listed as primary are fundamental since each factor in sufficient grade can produce clinical edema unaided by other forces The contributory factors on the other hand do not themselves produce edema but modify the severity or distribution of edema produced by one of the primary causes There are undoubtedly other factors in addition to those listed since it has been observed that in nephrosis a copious diuresis may begin spontaneously and massive edema can disappear even while the plasma proteins are still extremely low Unravelling the mechanism responsible for this spontaneous resolution of edema may well provide a diuretic more physiological and more constantly effective than those now at our disposal clinically

The maintenance of fluid balance, with all its physical niceties of adjustment, is only one of the functions of the circulatory system. In certain tissues the rate of blood flow must at times be increased to 20 or 30 times the resting rate in order to compensate for tissue activity, change in posture, temperature control or local inflammatory reactions.

Capillary blood pressure and flow, as might be expected, vary together over very wide ranges.¹² Blood pressure changes in the same capillary from moment to moment and may differ widely in adjacent capillaries arising from the same arteriole. For example, chemical injury to the frog's web produces reflex vasodilatation, increased rate of blood flow and a conspicuous rise in capillary blood pressure.²² Similarly, in man, heating the skin at the base of the finger nail induces hyperemia and with it a striking rise of capillary blood pressure in the heated area.¹¹ Cold, on the contrary, produces an initial vasoconstriction and decrease in capillary pressure followed after a few minutes by local reactive vasodilatation, hyperemia and elevation of capillary blood pressure. Raynaud's disease is a condition in which a more or less prolonged period of vasospasm is followed by arterial relaxation and reactive hyperemia. During the period of spasm capillary blood pressure is habitually low, e.g. 7 mm Hg, but with vasodilatation rises for brief periods to exceed 40 mm Hg.²³ Spontaneous variations in peripheral blood flow and capillary blood pressure are, under proper conditions, equally large. Clinical medicine uses this wide physiological range of peripheral blood flow to differentiate those peripheral vascular diseases characterized by pure vasospasm from those associated with organic or structural diseases of the arterial wall.

The development of simple thermo-electric methods of measuring skin temperature under standard conditions has made it possible to estimate deficiencies of blood flow and to differentiate the ischemia of vasospasm from that of obliterative arterial disease. Complete dilatation of structurally normal blood vessels elevates skin temperature to levels which are constant enough to be used as a practical estimate of the maximum increase in peripheral blood supply that can be produced by suitable therapeutic measures. The diagnostic methods available for producing temporarily maximal blood flow in the extremities are numerous,—novocaine block of peripheral nerves, general or spinal anesthesia, paravertebral injection of novocaine, or warming the body.²⁴ If skin temperature can be elevated by any one of these methods to 30.5° C or more, significant organic vascular occlusion is absent. The diagnoses to be considered are by this test limited to those conditions due principally to vasomotor disturbances.

If, during a vasodilator test, skin temperature rises only to 26 or 27° C, structural disease of the arterial wall is present in slight grade, and the organic vascular conditions must be considered. A partial vasodilator response reveals also that moderate arterial dilatation is still possible and considerable assistance may be expected from vasodilator agents including heat, typhoid vaccine, drugs and sympathetic ganglionectomy. It should

be mentioned that even in uncomplicated Raynaud's disease cervico-dorsal sympathetic ganglionectomy has been followed in some instances by perplexing recurrence of vasospasm. Smithwick, Freeman and White²⁵ have found the denervated vessels of these patients to be abnormally sensitive to epinephrine, thus extending to human beings the results of earlier studies by Langley, Meltzer and Elliott, on the abnormal physiology of mammalian blood vessels after degeneration of the post-ganglionic sympathetic fibers.

In advanced organic vascular disease the physiological variability of blood flow in the extremities may be almost or completely absent. At this stage abolition of vasoconstrictor tone fails to elevate skin temperature. Those therapeutic procedures which depend on vasodilatation cannot be expected to increase blood flow significantly. For treating patients with advanced organic vascular obstruction it was suggested simultaneously on physiological grounds by Landis and Gibbon,²⁶ and on clinical grounds by Reid and Herrmann²⁷ that varying the air pressure about the affected extremity might aid blood flow by physical means. Objective studies indicated that blood flow could be increased at least temporarily in this way, even though advanced organic arterial occlusion prevented increasing blood flow by other methods.

From this brief review of the clinical problems of edema and peripheral vascular disease it seems evident that the recent rapid advances in theory and practice have arisen from the interplay of thought and observation simultaneously in the fields of vascular physiology and clinical medicine. Theory, experiment, observation and conclusion follow logically though their origins include laboratory and clinic. The respective contributions of physiology and medicine are not in any sense separable, on the contrary, their interdependence is striking.

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ERRORS IN CARDIOVASCULAR ROENTGEN-RAY INTERPRETATION

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ERRORS in cardiovascular roentgen interpretation are due mostly to the following reasons. Insufficient knowledge of the theoretical and applied physical principles of the roentgen-rays, insufficient knowledge of anatomy, physiology and pathology of the cardiovascular system, and deficiency in the technical outfit and procedures.

Facts which pertain to the roentgenological study may not be registered and therefore the first part of the report, which should contain all findings, is inadequate. Or facts are registered but interpreted erroneously and therefore the second part of the report, which should contain the conclusions, is inadequate.

The limitations of the roentgenological method permit one to analyze and evaluate only certain aspects of the cardiovascular system, and these are not in all cases necessarily the most significant.

Every study should start with fluoroscopy. A film record in its frozen aspect expresses the statics, while fluoroscopy expresses the dynamics of the situation. Adaptation of the retina is of utmost importance, it increases in darkness in the form of a logarithmic curve, the knee of which is not reached until 15 to 20 minutes have elapsed. Information as to detail is enhanced by excluding much of the secondary radiation. This is done by using a small shutter. This may be the only means which will permit detection of small lime salt deposits in the heart or in the pericardium.

Since we are dealing with objects in motion, the exposure time of the film, taken at the conventional distance of 200 cm, should not be more than one twenty-fifth of a second. If one is dealing scientifically with heart size or when the amplitude of the pulsations is to be measured, it is indispensable to know in which phase of the cardiac cycle the roentgenogram was made, methods must also be employed to always guarantee the same phase of respiration. Ordinary teleroentgenograms do not represent a projection of the true size of an object, the degree of magnification is determined by the object-film distance, by the size of the object and by the target-film distance. The magnification of the projection of an average normal heart amounts to approximately 10 per cent.

Orthodiagraphy requires great accuracy, the silhouette should be drawn in diastole and during quiet, shallow respiration. Drawings and films should preferably not be made at the end of deep inspiration, a distortion of the silhouette results and even an involuntary Valsalva test may be produced.

* Read at the Detroit meeting of the American College of Physicians, March 3, 1936.
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Such chest films taken in deep inspiration have been partly responsible for the sweeping statements as to the smallness of the heart in the presence of tuberculosis of the lungs

Orthodiagraphic tracings can hardly ever be accepted as records for purposes of comparison and teleoroentgenograms only rarely so, unless certain standards are preserved. They are: The target-film distance must be maintained inviolate, the target, the mid-line of the patient and the mid-line of the film must be accurately centered, the chest must not undergo any change in position, either in the sense of (a) rotation along its long axis, or (b) increased lordosis or kyphosis. Furthermore, the position of the diaphragm and the phase of the cardiac cycle must be identical.

Roentgenology furnishes convincing evidence that there is no single type of visceral anatomy and physiology. Normality, as a statistical concept, refers to the average or central values on the curve of variability. Because of the range of variation, errors in interpretation occur and organic disease is occasionally diagnosed when none is present, while such disease is not recognized when it exists. This refers especially to the extreme constitutional types. In the hypersthenic type, enlargement of heart and aorta or aortic configuration is liable to be diagnosed while in the hyposthenic type, smallness of the heart or mitral configuration is often mentioned. The influence of the filling of the heart on its size is perhaps underrated and the constitutional factor often too greatly stressed, certain small hearts are small only when the examination is limited to the vertical position. Normal hearts show definite anatomical variations in their general shape independent of their volume. It is well to know that the size of the aorta increases continuously with age and the direction of the aortic arch changes. Elongation, dilatation, and tortuosity have been diagnosed and attributed to atherosclerosis where only anatomical-physiological changes due to age were present. Atherosclerosis, on the other hand, may be present without appreciably altering the size and shape of the vessel.

From the outer left caudal surface of the pericardium, a triangular ligamentous fold extends to the diaphragmatic and mediastinal pleura, after puberty, fat is found along its anterior surface. Ordinary chest films often do not permit differentiation of the heart shadow proper from this anatomical formation which, when included in the cardiac measurement, results in erroneously high figures.

The roentgenological lung pattern is fundamentally caused by the blood-filled vessels. They appear partly in length and partly in cross-section. These structures, especially when blurred because of improper exposure technic, have been erroneously interpreted as pulmonary fibrosis. The following three abnormal appearances of the lung fields have often been misinterpreted. First. The active, hypertensive, interstitial and intra-alveolar edematous transudation, of a subacute type and predominantly central location which occurs especially in the course of acute or chronic azotemic cardio-renal disease. This condition has not the appearance of vascular dilatation,

and should therefore not be designated as congestive failure, and it is not inflammatory in type though it has been called pneumonic infiltration. Second A passive, hypertensive, arterial, venous and lymphatic enlargement, with interstitial reaction, of a chronic type and diffuse appearance, which occurs most typically in the presence of chronic mitral valvular lesions. It has been confused with fibrosis, milary tuberculosis and carcinomatous disease of the lymphatics. Third An active, hypertensive enlargement of the pulmonary arterial tree, as it is observed in instances of pulmonary atherosclerosis, arteriosclerosis and syphilitic arteritis, or in the course of pulmonary artery orifice regurgitation or interatrial septal defect. It is often described as evidence of congestion or infiltration and the unduly outstanding shadows of the main branches have been interpreted as tumors, especially of the metastatic type.

One must realize, in studying the pulsations, that they express a combination of volumetric, pressure and displacement changes. Only the outer pulsations of the silhouette can be studied under normal conditions and the pulsatory movements of the following structures are not visible, under normal conditions. A portion of the anterior heart surface, the atrio-ventricular septum (the piston-like movement as contrasted with the margin movement), the first portion of the ascending aorta in its whole circumference, the mesial contours of the distal portion of the ascending aorta, of the arch of the aorta and of the pulmonary artery, a considerable portion of the lower heart border. The visible pulsations of the aorta do not express exclusively actual volumetric changes but represent position changes of the whole vessel. The actual amplitude of the movement is fully registered only when its direction is at right angles to the direction of the central rays. It may be added that the roentgenological ventricular systole, in the conventional sense, represents the emptying periods of the ventricular systole.

Much information is missed without a fluoroscopic study. The absence of movements along the silhouette border is of significance in the diagnosis of myxedema, cardiac tamponade and certain types of chronic adhesive-constrictive pericardial disease. However, it should be pointed out that in other types of the latter lesion, a great amplitude can be observed, especially with a rapid diastolic outward movement and usually associated with marked chest wall pulsations. They are found first when there are external adhesions fixing heart and pericardium to the anterior chest wall, and second when the base of the heart is fixed, then the longitudinal contraction of the ventricular cone is interfered with and this reduction in movement is compensated for by increased marginal excursions. A diminution of pulsations along the left lower heart border is observed whenever the latter is formed by the right ventricle. One observes in the course of severe emphysema an inspiratory distention, followed by an expiratory diminution of the silhouette more marked on the right side. Intracardiac calcifications in the atrio-ventricular septum and in the valve rings are sometimes diagnosed only by observing the characteristic dancing movements. The presence of even a

small amount of air or gas along the mediastinal surface of the lung is immediately diagnosed by the large, flopping pulsation of the silhouette border showing also a vertical, "heaving" component

An aneurysm of the ventricular muscle can sometimes be diagnosed only by observing abnormal pulsations, namely the outward movement during systole (simultaneously there appears a clinical thrust) or a synchronous or paradoxical movement as compared with the adjacent cardiac contours. The right ventricle may form a greater portion of the left silhouette contour and increased pulsations are noted in the presence of increased output (tricuspid or pulmonary regurgitation). The concomitant aortic pulsations remain small, however, indicating that the increased movement was not caused by left ventricular action.

Increased pulsations along the pulmonary arch, not necessarily associated with undue prominence, may direct the attention to the possibility of a thyrotoxicosis or patency of the ductus arteriosus. Expansile pulsations of the pulmonary artery branches indicate a wide pulse pressure in the lesser circulation, these findings do not accompany a relative regurgitation. A stiff-walled aortic vessel may reveal a marked shift in toto.

Measurements attempt to establish standards of normal and thus help to decide whether or not a given case is within the range of normal variation and if not, to give mathematically the degree of deviation from normal. It must be understood that cardiac size and shape within the range of normal variation may well coexist with disturbed function, coronary artery disease and constrictive pericardial disease may be cited as examples. Because of the range of normal variation, no sharp distinction can be drawn between findings in the upper normal range and those in the incipient abnormal stage, and a heart which is originally small may enlarge considerably before it exceeds the upper limit of normal. Also the muscular wall may increase in thickness without producing appreciable alterations in shape and size of the silhouette. The application of average figures is of limited value since we are dealing clinically with one individual, and the use of absolute figures likewise is of little practical use, such figures must be correlated with other characteristics of an individual, introducing coefficients of correlation. Standards derived from people in the best of physical condition are not quite the same as those of the average population. Furthermore, one cannot compare orthodiagraphic with teleroentgenographic standards. The common methods of measurement stress the formal-quantitative side and are insufficient as to the functional-quantitative aspect.

Unless calcification is present, no reliable method of accurately determining the size of the ascending aorta exists. A normal aortic size is compatible with a marked degree of hypertension of long duration.

No determination of heart size short of the actual volumetric reconstruction is correct. The antero-posterior dimension of the heart, the depth, must be considered. The correlation coefficient between heart size and external somatic measurements is too low to have great statistical signifi-

cance The transverse diameter and the cardio-thoracic ratio are poor criteria since they depend too much on body build

Much interest is attached to possible changes in the size of the silhouette as one may observe it in the course of infectious disease, under the influence of therapy and during physical exercise and pregnancy One hears statements that a failing heart has diminished in size as compensation became restored This is possible Often, however, pericardial fluid has been merely resorbed or the position and shape of the heart have changed as the size of the liver decreased One should likewise look with much doubt upon statements that an aneurysm of the aorta became smaller in the course of antisyphilitic therapy And one will commonly find in comparing two films of the same patient, taken at different times, that the criteria for correct comparison are not given It is almost impossible to make a roentgenologic study while exercise is being continued, and following strenuous exercise an identical position of the diaphragm, of the chest and of the cardiac cycle is rarely obtained Because of the marked physiologic changes which take place immediately following exercise, one is not permitted to draw conclusions as to the changes which might have taken place during the exercise Pregnancy carries with it a shift of the center of gravity which results in a change in the body position and therefore in the projection of the heart

Much information is missed when the oblique and lateral views are not used This may be illustrated by a few examples It has already been mentioned that the antero-posterior dimension of the heart is of significance This is especially true in instances of displacement of the heart due to deformity of the chest wall An isolated prominence of the conus arteriosus, the outflow tract of the right ventricle, or an enlargement of the left atrium may be visualized only in an oblique view The anterior view may reveal an enlargement of the heart to the left while the oblique or lateral views indicate which ventricle predominates Small aneurysms of the aorta, an encroachment of an aneurysm on the trachea and esophagus, erosion of the spine due to aneurysm, certain types of calcification in the pericardium, coronary arteries, in the descending thoracic and abdominal aorta, coarctation and right-sided course of the aorta are thus diagnosed

Certain terms like mitral or aortic configuration are somewhat misleading These terms are purely descriptive and do not necessarily indicate that the respective valves are affected Thus we find a straight or convexly prominent middle portion of the left cardiac contour often in association with a poorly visible aortic knob not only in mitral valvular disease but also in the following conditions In the hyposthenic constitutional type, in emphysema, in thyrotoxicosis, in certain congenital or acquired lesions of the pulmonary artery, and in the presence of right convex scoliosis of the spine And we find a prominence of the aortic shadow, a prominence of the left lower contour together with a deepening of the waist of the left contour not only in aortic valvular disease but also in the following conditions In the hypersthenic type, together with a high position of the diaphragm,

among aged individuals, and in many instances of hypertensive and atherosclerotic disease. A pseudo-aortic configuration is represented by the wooden shoe type of heart, as observed with the tetralogy of Fallot.

One often speaks of cardiac dilatation where it would be more correct to say enlargement of the silhouette. This applies to instances of moderate degrees of pericardial effusion of different etiology including myxedema and glomerular-nephritis. The enlargement of the silhouette may also be caused by the thick fibrous layers of adhesive-constrictive pericardial disease. Excessive degrees of hypertrophy without any dilatation, likewise, cause enlargement of the silhouette. Often the roentgen examination will shed no light on the different etiologic factors of cardiac dilatation which may as easily be caused by diphtheria, myxedema, beri-beri, arterio-venous anastomosis or a combined valvular lesion. Neither is it possible to correlate the degree of dilatation with the efficiency of the heart muscle. For this, the determination of the work of the heart as expressed by stroke or minute volume has a higher statistical significance. However, it is of value to determine whether the dilatation predominantly affects the ventricular or the atrial mass. The silhouette of the heart, in an instance of left atrial enlargement of excessive size may fill the chest cavity transversely and yet a fair function of the circulation may be maintained for a long time.

The roentgenological picture of a pericardial effusion of a marked degree is rather characteristic, but it may be rendered quite atypical by localized obliterations of the pericardial cavity. If the superior recessus is affected, the shortening of the vascular shadow to a short pedicle does not result. Obliteration of the pericardial space along the cardiac surface results in subdivisions in the silhouette contours. In both instances, therefore, cardiac enlargement rather than pericardial effusion may be erroneously diagnosed. Old encapsulated right-sided exudate has been confused with an aneurysm of the proximal portion of the aorta because other roentgenological and clinical signs of chronic adhesive pericardial disease had been overlooked.

It is not correct to assume that oblitative, adhesive and constrictive pericardial disease necessarily leads to cardiac dilatation, as a matter of fact one may find a rather small silhouette and the constrictive process may even counteract an enlargement of the left atrium in the presence of mitral disease or of the left ventricle in the presence of aortic valvular disease.

The very first part of the ascending portion of the aorta cannot be visualized (unless its borders are outlined by lime salt deposits) and therefore a fusiform enlargement as well as a small saccular pouch may escape observation. Because of the same invisibility, small pouches which develop from the arch either from its convexity in a cephalic direction between the brachio-cephalic vessels or from its concavity in a caudal direction may be completely missed. Often the aorta of younger individuals, who are affected by a marked degree of aortic valvular regurgitation or by a marked increase in the systolic and diastolic pressure, is found to be dilated. This should be considered as a dynamic dilatation and preferably not diagnosed as

an aortitis or aneurysm. Those rare aneurysms of the ascending aorta which develop forward and to the left are readily confused with lesions of the pulmonary artery, particularly since they give rise to clinical signs and symptoms at the left side of the mid-line. In the differentiation of thoracic aneurysm from other mediastinal masses, the following points are of value. Views from different angles will show whether in some the mass can be definitely shown separate from the aortic shadow and likewise whether in some it is a definite outgrowth from the aortic shadow, in aneurysm the adjacent portions of the aorta will usually show some widening, in aneurysm the chief axis of the mass is determined by two forces, that of gravity and that of the systolic impact, and finally in aneurysm the contours are often lightly outlined in shell-like fashion by lime salts.

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ROENTGENKYMOGRAPHY ITS CLINICAL AND PHYSIOLOGICAL VALUE IN THE STUDY OF HEART DISEASE *

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UNTIL recently the fluoroscope has been the only clinical means for routinely investigating the functional movements of an organ or structure. Frequently these movements are so small and quick that they cannot be accurately registered by the eye. The crystals of barium-platino-cyanide in the fluoroscopic screen produce a "lag" and "afterglow" which make it impossible to observe accurately fast movements. Furthermore, the only records of such studies are the subjective notes of the observer. Attempts to determine the time occurrence of related movements are very difficult, particularly in roentgenoscopy of the heart. Cinematography is now possible but the procedure is complicated, expensive, and is as yet unsatisfactory for daily use. In 1911 a Polish physiologist, Sabat,¹ adapted the moving slit camera of the physiology laboratory so that it could be used to study the movements of the heart by the roentgen-ray, and thereby inaugurated a new and accurate method for graphically recording functional movements on a single film. Independently of Sabat's work, Gott and Rosenthal² of Munich in 1912 devised a similar apparatus and named its application "Rontgenkymographie." In 1916 A. W. Crane³ compared his kymographic tracings with polygraphic and electrocardiographic waves. Robert Knox⁴ of London in 1922 contributed the next paper on kymography, and in 1925⁵ suggested its application to the investigation of esophageal and gastric peristalsis. Knox, like the others, was handicapped by the lack of sufficient electrical energy for the production of convincing radiograms. These earlier workers employed from one to four slits, which made it possible to record only that number of points on the heart's surface. To Pleikart Stumpf⁶ of Munich belongs the credit for developing the modern kymograph, as it was he who in 1928 introduced the use of a grid with multiple slits sufficient in number to reproduce the general outline of the structure. I. Seth Hirsch⁷ of New York in 1934 introduced Stumpf's work to American roentgenologists and made original contributions of his own, particularly in recording simultaneously the heart sounds, the electrocardiogram and the kymogram.

PRINCIPLES AND TECHNIC OF KYMOGRAPHY

It must be understood that the kymographic method records only movements at certain points on the border of the heart. These points are small,

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are equally spaced, and correspond to the width of the slit in the grid—namely 0.4 mm. The grid* is a large sheet of lead in which the slits are cut horizontally and it is placed next to the patient's thorax (figure 1)

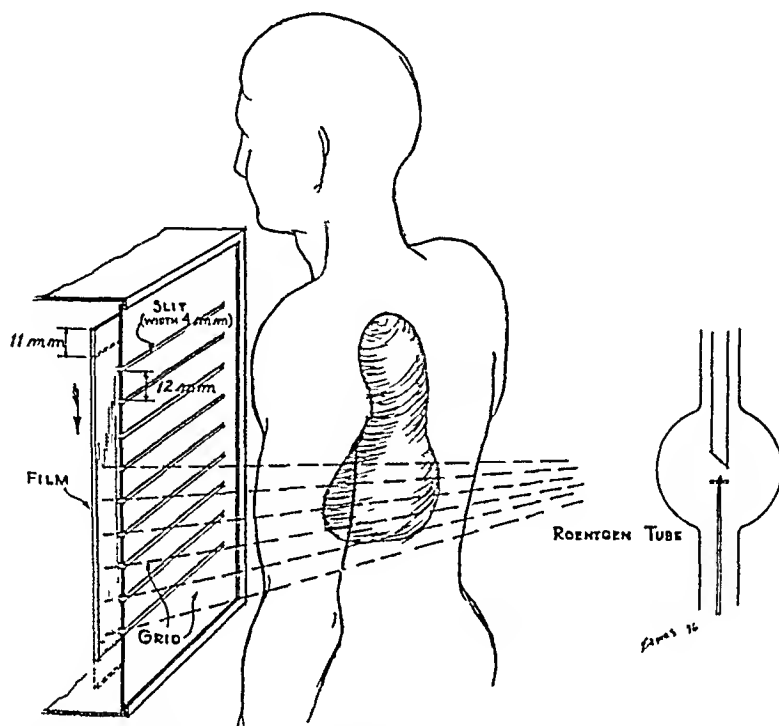


FIG 1 Diagrammatic sketch of kymograph. In this arrangement the grid is fixed, the film moving downward during the exposure and the kymograms appear as in figure 2. Another method is to move the grid at the time of exposure with the film remaining stationary. (Modified after Stumpf.)

The slits must be sufficiently close together so that on looking through them it is possible to recognize the shape of the organ the movements of which are to be recorded. Generally, slits placed 12 mm apart are suitable. During a single continuous exposure of 1 + second the film is moved downward behind the fixed grid a distance slightly less than the grid spacing—actually 11 mm. This explains the narrow white lines which divide the kymogram into frames and also prevent an overlapping of exposures (figure 2). It is well to emphasize that each frame is a record of the movement of a very small segment of the heart border registered on 11 mm of film.

By this procedure the varying shape of the heart at any instant in its cycle is reproduced on the film. The marginal contour of the heart is recorded in a wave-form, because the movement of the margins is a lateral expanding and a medial contracting thrust. Occurring simultaneously with the marginal movements are changes in the density of the heart shadow corresponding to systole and diastole. They are shown as transverse bands, the better illuminated representing systole and the less illuminated diastole. Parts which do not move are reproduced as straight lines parallel-

* A detailed description of the kymograph is given in references 7, 13, 21, 22



FIG 2 Kymograms of a normal heart

(a) With slits horizontal for registering lateral movement—film moved downward
On the left border in frames 8-14 are the waves of the left ventricle, frames 6-7 left auricle, frame 5 pulmonary artery, 1-3 descending aorta. Over the right border in frames 10-12 are waves of right ventricle, frames 7-9 right auricle with superimposed ventricular waves

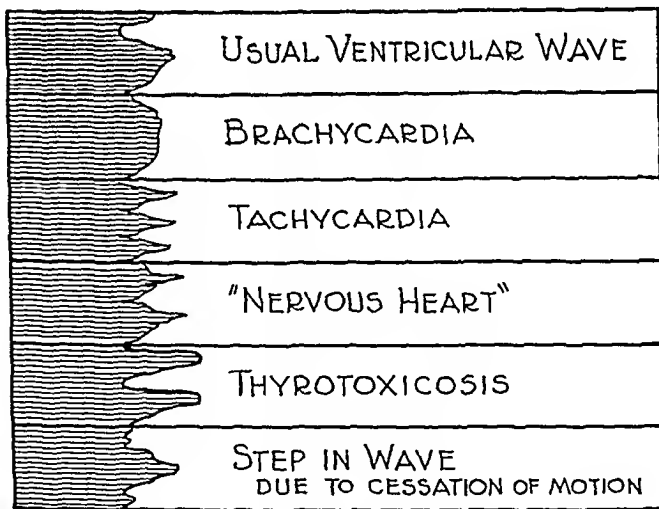
(b) With slits vertical to record vertical movement—film moved horizontally
Frame 1 shows right ventricular waves, frame 2 composite left auricular waves, frame 6 aorta, frame 7 pulmonary artery, frame 8 left auricle, frames 9-11 left ventricle

The white horizontal lines which divide kymogram into frames are the unexposed portions of the film. The points on the ribs and diaphragm which overlie a slit appear as step-like shadows. The pulmonary markings are shown as wavy lines. The contour of structures without movement or possessing movement in a direction perpendicular to the slits is recorded as vertical lines. Characteristic waves are seen over the borders of various chambers and great vessels

ing the direction of the movement of the film. The kymogram thus shows the size and outline of a structure and graphically registers the movements of numerous individual points that are evenly distributed over the margins of the structure radiographed.

THE READING OF KYMOGRAMS

The size and shape of the heart or structure radiographed are analyzed in the same manner as are teleroentgenograms. The trough of the wave is that particular point at maximum systole, while the peak of the wave is the same point at maximum diastole. (Figures 2A and 2B.) The lower leg of the wave represents the diastolic phase of the cardiac cycle while the upper leg represents the systolic phase. If all the peaks are connected by one line and all the troughs by another, two outlines are obtained with a space between them which Stumpf^{8,9} has termed the "Movement Space" of the heart. For practical purposes the inner line represents the systolic, the outer the diastolic, size. The character of the "Movement Space" varies with individuals, but remains constant for the same person under the same conditions. It should be stressed that the amplitude of the waves is an accurate measure of the change in cardiac volume only when the heart border is exactly at right angles to the slits and rotates about a central and vertical axis.



TRACINGS OF VENTRICULAR WAVES
PRODUCED BY DIFFERENT TYPES OF MOTION

FIG 3 Tracings of ventricular waves produced by different types of motion

The individual waves show a marked degree of variation. When the movement is rapid the contour of the curve tends to parallel the slit. During slow movement the film travels a definite distance and an oblique line is formed. A cessation of movement is shown on the contour of the waves as a step formation (figure 3). Over the ventricles and great vessels the

waves are asymmetrical. That is, one leg is rectilinear and the other oblique, which means that the movement is quick in one direction and slow in the other (Review figure 2 and figure 3)

Figure 4 illustrates the method of comparing the time occurrence of movements at different points by tracing the various waves on a sheet of

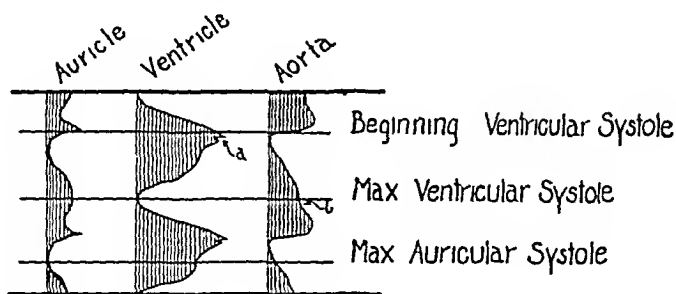


FIG 4 Diagrammatic representation of the time relationships of movements occurring simultaneously in ventricle, auricle, and aorta

The diagram illustrates the method of comparing the time occurrence of movements at different points by tracing the waves on ruled paper. The tracings are begun at the white lines at the lower edge of the various frames. The time correlation is then facilitated by drawing parallel lines.

Notch (a) coincides with the first heart sound, and indentation (b) with the second sound (Hirsch)

ruled paper. The tracings are begun from the white lines at the bottom of the various frames. The time correlation is then facilitated by drawing parallel lines. Thus it is readily appreciated that the straight limbs of the ventricles and great vessels occur at approximately the same time but run in opposite directions. The quick movement of the ventricle is from without inwards, during systole. In the aorta and pulmonary arteries the quick movement is from within outwards due to their sudden filling by ventricular systole. The bend on the diastolic limb of the ventricular wave corresponds to the beginning of auricular systole. Likewise at the time of auricular systole the ventricle has attained only $2/3$ to $3/4$ of its maximum volume. This fact, namely that auricular systole is an important and effective hemodynamic force, confirms the ingenious experiments made by Gesell¹⁰. His extraordinary work was done in Erlanger's laboratory. We are indebted to the latter for many helpful suggestions.

Since the film is moved at a uniform rate of speed, every millimeter which the film travels will correspond to a definite period of time. With this technic the film moves 11 mm during an exposure of 1 second and a distance of 1 mm will then correspond to $1/11$ of a second. In each frame the recording of the waves always begins at the lower edge and ends at the top. Thus by measuring with calipers or a square of ruled glass⁸ the distance from the beginning of the record to any desired point on a wave and marking this same distance in another frame, the time occurrence of the movement in question can be determined (figure 4). The outward movement of the aorta is usually a good starting point for studying the time

and duration of the heart cycle. In the same manner the time required for systole and diastole in a cardiac cycle can be determined.

By simultaneously recording the heart sounds and kymogram⁷ it can be similarly shown that the first sound coincides with a notch on the systolic limb of the ventricular wave. The second sound corresponds to the end of ventricular systole and is registered as an angulation on the retraction wave of the aorta (Figure 4). Lack of space prohibits a further discussion of physiological facts obtained from kymograms.

CLINICAL APPLICATIONS OF KYMOGRAPHY

In cardiology the kymogram offers two sources of information. (1) It identifies the topographical position of the chambers of the heart and great vessels as each part produces characteristic waves. (2) It permits a study of the amplitude, course and time relationships of the various movements in normal and pathological hearts.

In considering the first point, it has been proved^{7,9,11} that in the erect position a majority of normal hearts show pure ventricular movements over the right lower border (figure 2). This area was formerly considered as part of the right auricle. In cases of mitral disease the extent of an enlarged left auricle is recognized by the auricular waves over the upper left heart border. The chambers constituting the posterior cardiac silhouette can be identified and their extent determined by taking a kymogram while the patient is swallowing an opaque meal. In this way the movements of the different chambers are imparted to the esophagus and can be recorded (figure 5).

A second source of information lies in a study of the type of movement recorded. This is best considered under two heads: (A) Changes in the movement as a whole, and (B) Changes in the form of individual waves.

(A) *Changes in the Movement as a Whole*. Stumpf^{9,12,21} has reported that with beginning hypertrophy of the left ventricle there is a widening of the "Movement Space" over the superior half of the ventricle. In left ventricular hypertrophy with myocardial damage the whole "Movement Space" is decreased, especially over the apex. However, there are also normal hearts in adults that have only a small lateral apical thrust. Lack of movement at the apex is a pathological indication only when confirmed by other signs or when the apical movement has changed in the interim between observations.

In diseases of the pericardium there is a marked reduction in the amplitude of movement. The case of adhesive pericarditis reported by Johnson¹³ revealed practically complete absence of motion over the left ventricle and right heart border with diminished aortic and left auricular waves. We include here a case of tuberculous pericarditis with similar findings (Figure 6). In the diagnosis of pleuro-pericardial-diaphragmatic adhesions the kymogram is of considerable value, as is demonstrated in figure 7. There

should be greatly reduced movements in the presence of calcification in the pericardium²¹

Bickenbach¹¹ and von Braunbehrens¹¹ have shown that characteristic changes occur in the movement over areas of cardiac infarction. The zone of infarction is recognized by the absence of motion in several frames,



FIG 5 Oblique kymogram of esophagus made while patient swallows a barium meal for purposes of identifying chambers constituting the posterior cardiac silhouette. Each chamber in the posterior silhouette transmits its characteristic movements to the adjacent portion of the esophagus.

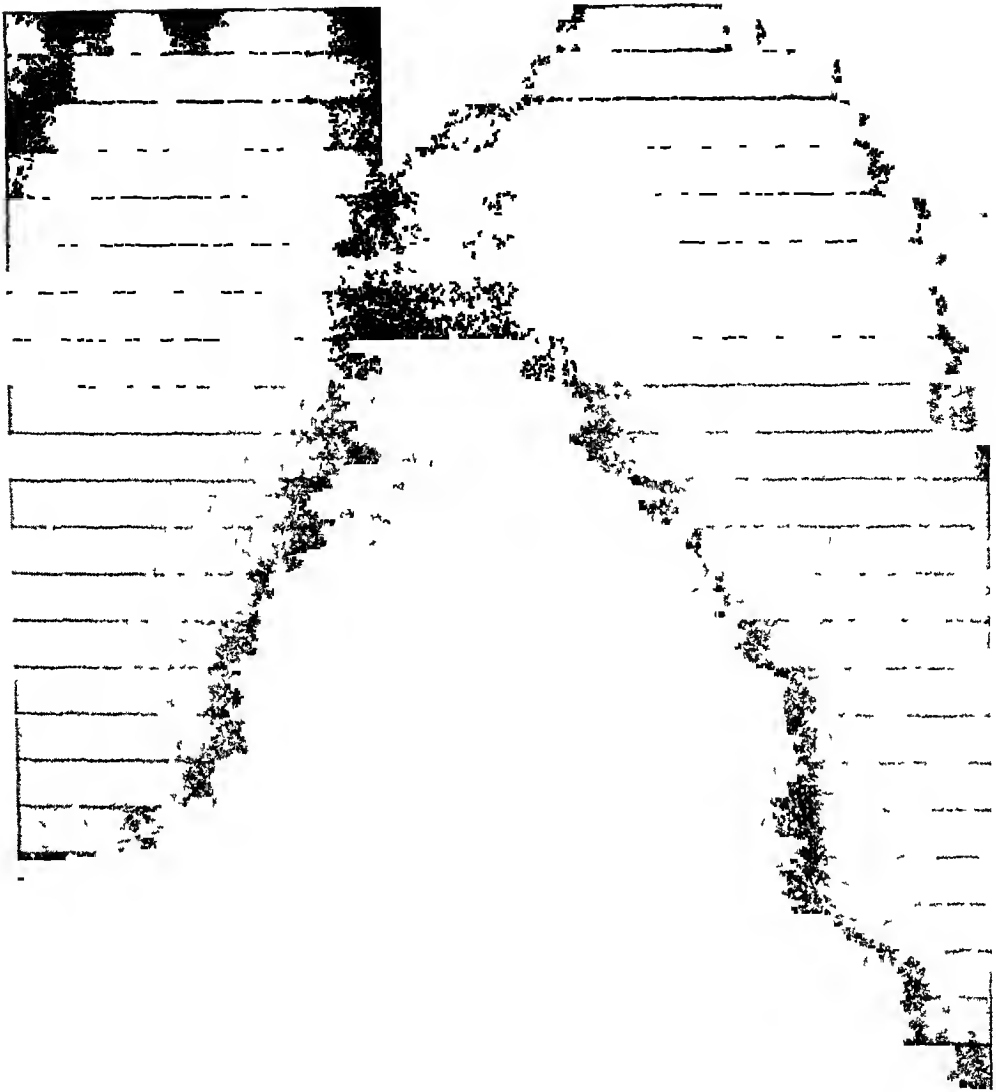


FIG 6 Tuberculous pericarditis. There is complete absence of movement over the left ventricle and lower portion of right heart as shown by the vertical lines in these frames. The auricular and aortic waves are feeble.

A 43-year-old white married foreman who worked in a grinding (sand) factory for 17 years, finally developing a silico-tuberculosis. On admission he was orthopneic, decompensated and critically ill. Heart was greatly enlarged, sounds were extremely faint, blood pressure 130/110, and there was a pulsus alternans. A series of eight pericardial taps was performed, removing a total of 1240 cc of yellow turbid fluid in which acid fast bacilli were demonstrated. Guinea pig inoculation was positive for tuberculosis. Following the first few pericardial paracenteses, air was reinserted, producing a hydropneumopericardium which revealed a thickened pericardium, in places $1\frac{1}{2}$ to 2 cm in thickness.

while there is ample motion in the frames directly above and below. We have observed a case which presented this picture, and the clinical evidence, including the electrocardiograms, conclusively confirmed the diagnosis of cardiac infarct (Figure 8). According to von Braunbehrens,¹⁶ an aneurysm of the ventricular wall gives paradoxical pulsations, i.e. the thin walls of the sac will show an outward movement during the medial contraction of ventricular systole.

In coronary heart disease the amplitude of the ventricular waves is noticeably diminished (figure 9). These observations are of significance only

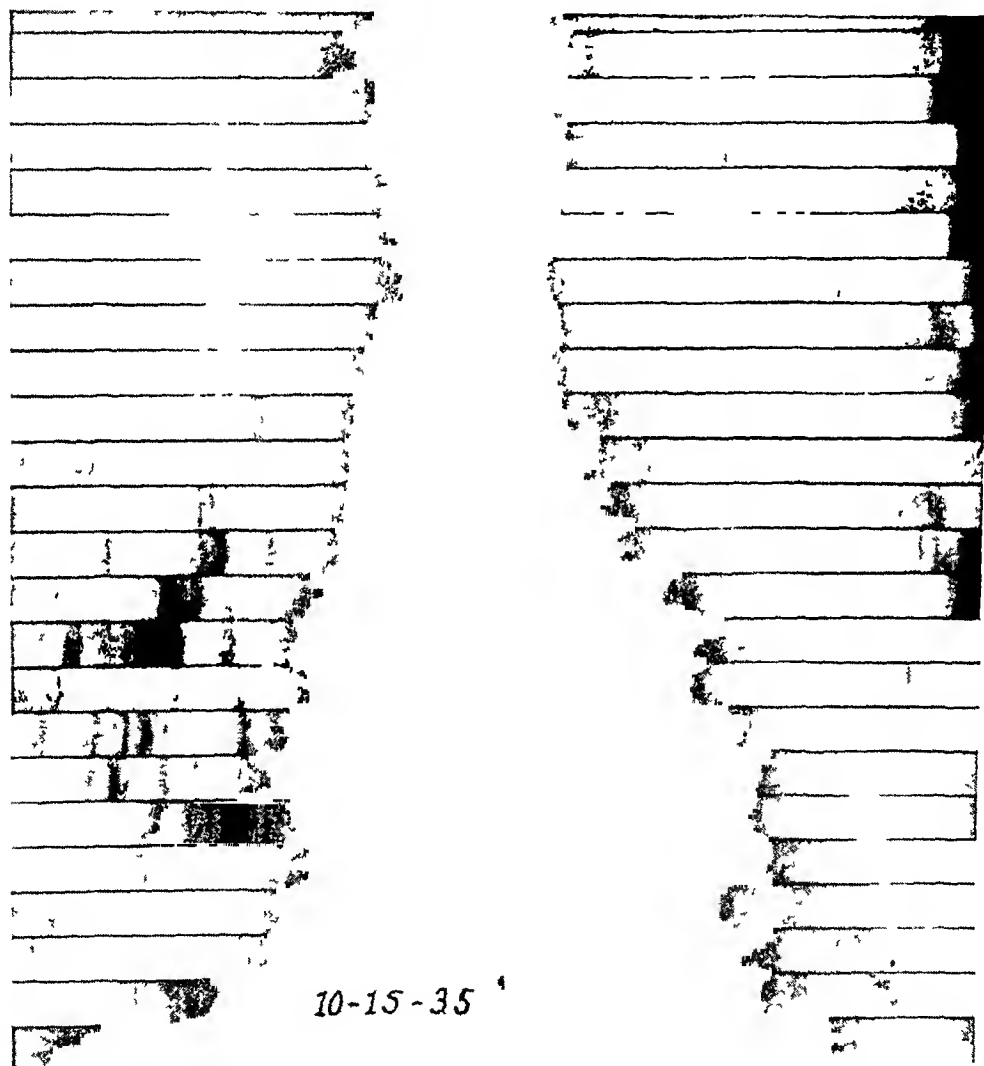


FIG 7-a

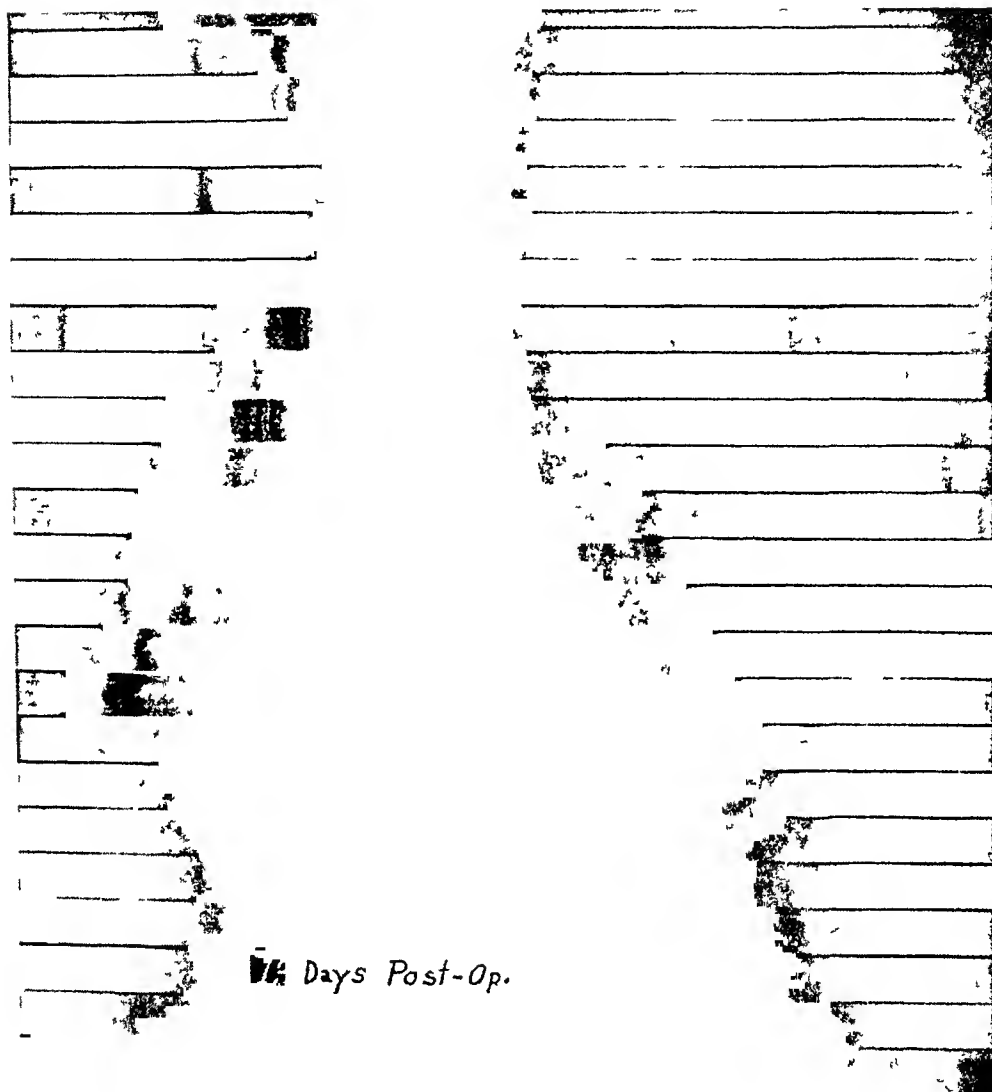


FIG 7-b

FIG 7 Kymogram showing presence of pleuro-pericardial-diaphragmatic adhesions
 (a) Shows absence of movement over right heart border as a result of pleuro-pericardial-diaphragmatic adhesions

(b) Illustrates the presence of movement 13 days after a cardiolysis of the old Brauer type Patient was a 36-year-old white married farmer who developed his first attack of rheumatic fever at the age of seven For past five years he had become progressively more dyspneic on exertion until at time of admission he could scarcely walk At that time he was decompensated and had signs of mitral stenosis and insufficiency with auricular fibrillation complicated by pleuro-pericardial-diaphragmatic adhesions over the right heart border After establishing cardiac compensation by digitalis, Dr Evarts Graham performed the old type Brauer cardiolysis, freeing a dense band of adhesions along the right heart border and sternum Recovery was uneventful and patient left hospital in two weeks greatly improved and can now do light tasks without becoming dyspneic

when associated with a straightening or sagging of the left heart border, as first reported by Levene and coworkers¹⁷

(B) *Changes in the Form of Individual Waves* The kymographic waves show a wide variety of forms even in normal hearts. This is especially true of the ventricular waves. Reports by other workers and a study of our own material have convinced us that at least three variations, and possibly a fourth, in the ventricular waves are characteristic of recognized cardiac disorders.

(1) In the so-called "nervous," "irritable" or "excited" heart disturbances,²¹ a sharp peak appears on the crest of the ventricular wave at the

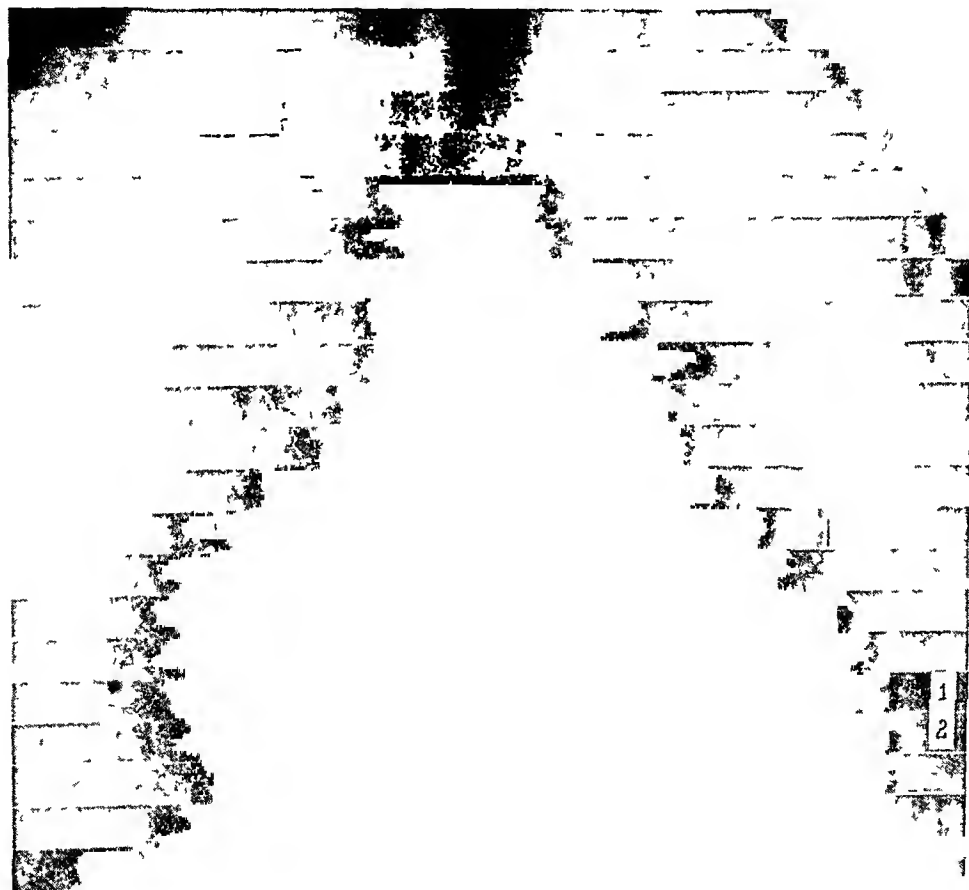


FIG 8 Infarct in ventricular wall shown in kymogram. The area of infarction is recognized by the absence of motion in frames 1 and 2 with adequate movement on either side.

White married Italian woman 60 years of age. Three weeks prior to admission she experienced a severe precordial pain which persisted. On admission she was cyanotic, orthopneic, and exhibited Cheyne-Stokes respiration. B P 112/70. Heart greatly enlarged. E K G showed auricular fibrillation and evidence of a coronary occlusion. Kymogram made six weeks after coronary accident.

beginning of systole (figure 10) This type of heart is found almost exclusively in individuals of the asthenic habitus

(2) In cases of hyperthyroidism, the waves are abnormally high and the period of systole is extremely short (figure 11) The waves are biconvex



FIG 9 Coronary heart disease There is a flattening of the outline of the left ventricle with a marked diminution in amplitude of the movement The waves are actually of less amplitude than those of the right ventricle

A 65-year-old man who had experienced extremely severe attacks of angina pectoris 2 to 3 times weekly for the past two years EKG showed evidence of myocardial damage Patient died suddenly five weeks later, presumably from a large cardiac thrombosis Post-mortem examination revealed an extreme degree of calcification in the coronary arteries

(3) In aortic insufficiency, there is an immediate and uniform filling of the left ventricle, which is shown as a continuous lateral movement (Figure 12) In advanced cases the amplitude of the waves is greatly increased

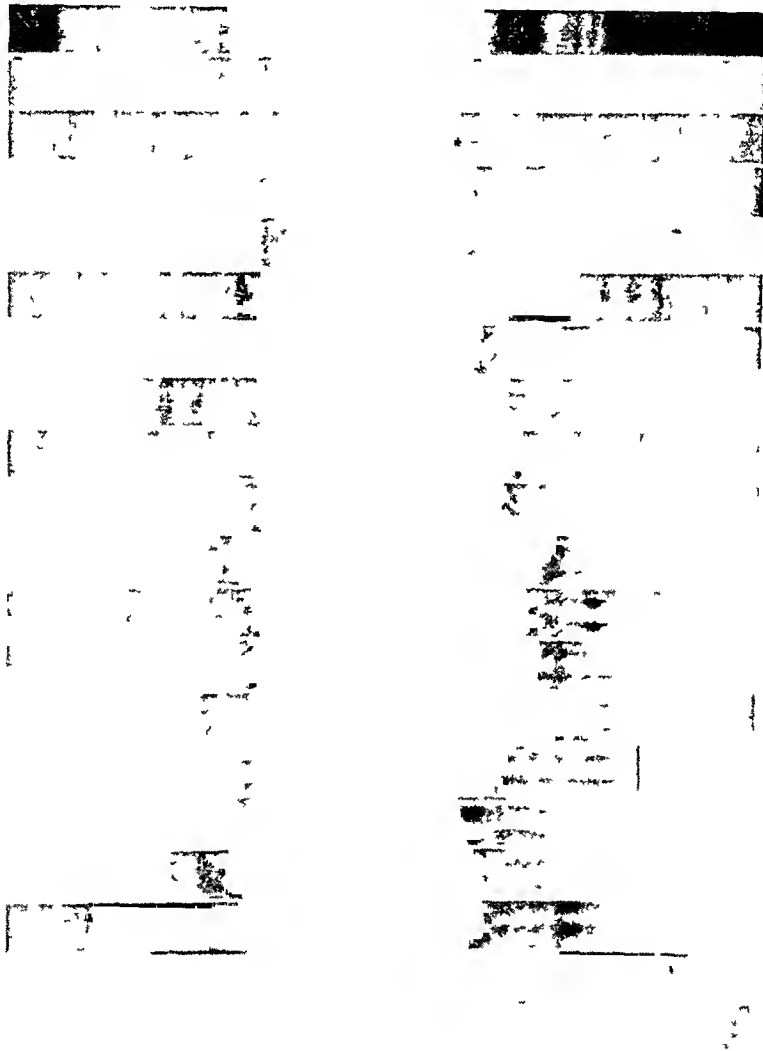


FIG 10 "The nervous heart" The additional little peak on the ventricular waves just preceding systole is characteristic of hearts easily excited

Hearts of this type are usually found in individuals of the asthenic habitus White married woman 27 years of age She was excitable, emotional and undernourished

(4) In myxedema, the ventricular waves are low and rounded and appear to be characteristic of this disturbance (figure 13) However, other types of myocardial degeneration may produce similar pictures although we have not seen them

Our study of cases with lesions of the mitral valve has been disappointing as the vibrations and alterations in the hemodynamics produce complex waves which are extremely difficult to analyze. In mitral lesions, the diastolic hmb of the left ventricle frequently appears as a smooth oblique line

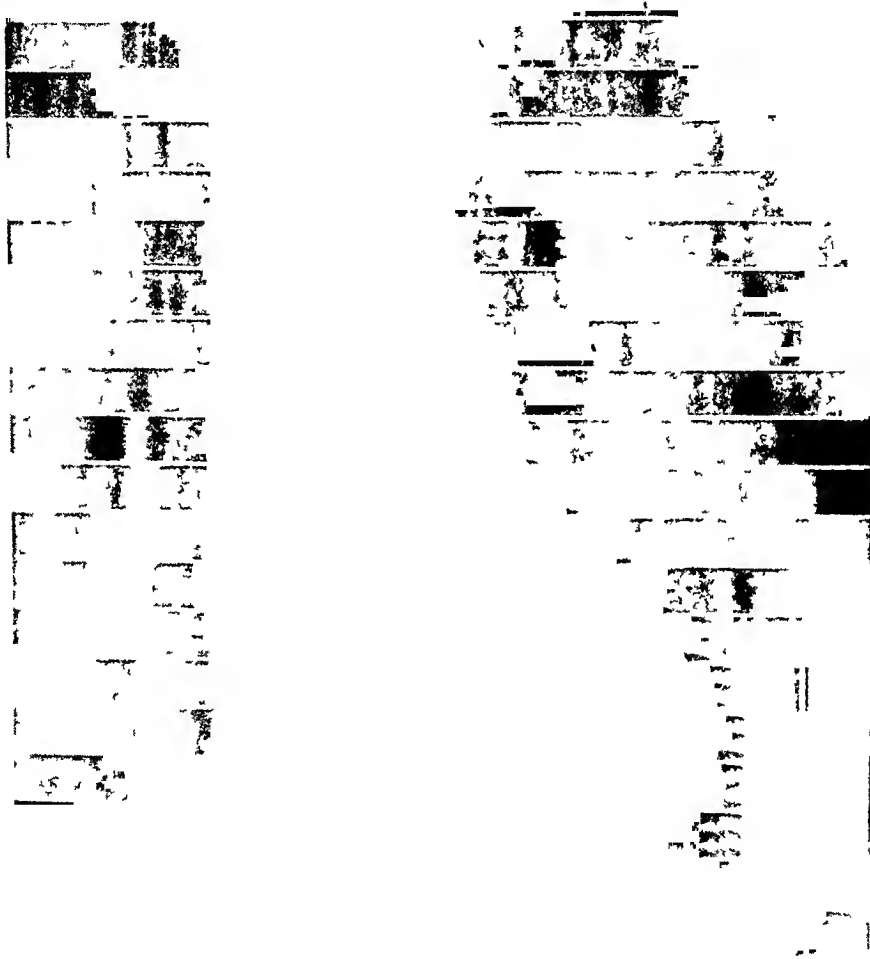


FIG 11 Heart in hyperthyroidism. Note the tachycardia, the generally increased amplitude of the waves and the short phase of systole. Ventricular waves are biconvex. Patient is a 50-year-old white male with exophthalmic goiter. Basal metabolic rate was + 56 per cent.

ending in a short plateau which precedes systole¹⁸ (Figure 14). Zdansky and Ellinger¹⁹ report that a characteristic auricular curve is present in mitral stenosis. We have been unable to confirm the consistent appearance of either observation.

The aortic waves exhibit pathognomonic variations in two cardiac dis-

orders, aortic regurgitation and aortic stenosis. In aortic regurgitation there is marked increase in the outward filling of the aorta and a very prompt emptying of the vessel as part of the blood rushes back into the ventricle. The curve is analogous to that of the Corrigan pulse (figure 12). With aortic stenosis the outward thrust becomes an oblique line as the aorta is filled slowly due to the narrowing of the orifice (figure 15). The period of ventricular systole is prolonged.

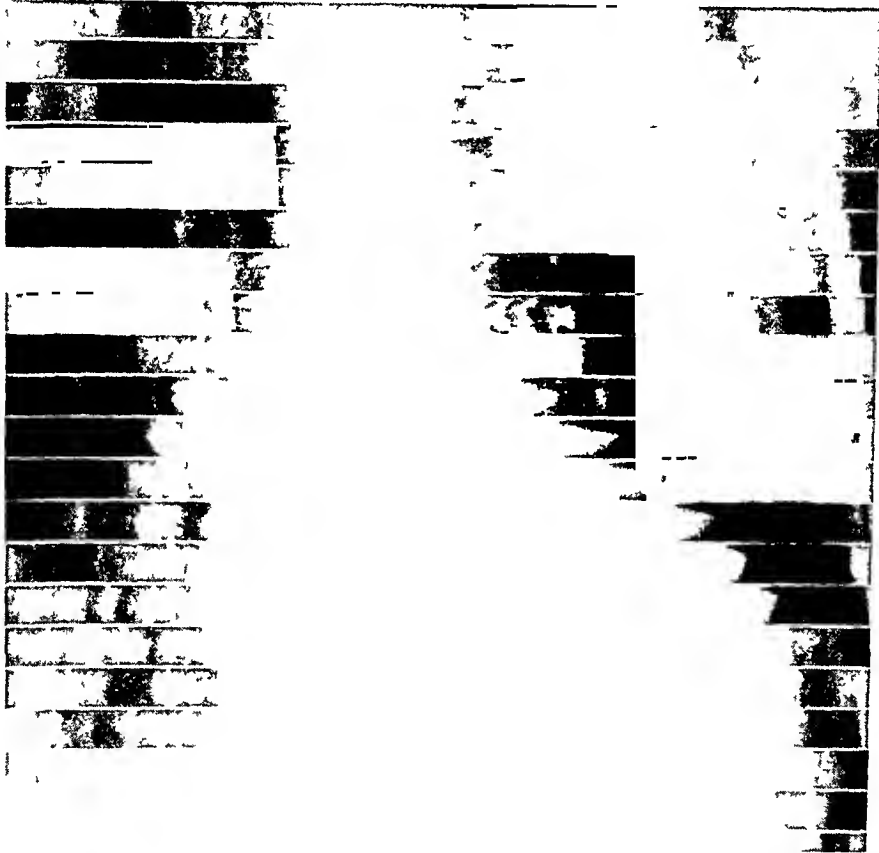


FIG 12 Aortic insufficiency. There is an immediate and quick filling of the left ventricle as shown by the straight diastolic leg. Ventricular and aortic waves are greatly increased in amplitude. The aortic wave retracts quickly and is analogous to that of the Corrigan pulse.

A 37-year-old white married woman, a known luetic who has been treated for six years. Aortic insufficiency present from time of admission. Five years ago patient developed syphilis of cerebrospinal meninges. B P 135/5. Wassermann test 4+. Heart greatly enlarged.

In aneurysms of the aorta, the amount of movement is variable and decreases with the volume of the blood in the sac, the size of the clot, and the thickness of the sac wall. Practically all aneurysms show movement, either intrinsic or transmitted. Kymograms of aneurysms of the ascending aorta reveal waves that are symmetrical, i.e., both the outward and the contracting forces are of the same type and produce a pyramidal-shaped wave.

(Figure 16 and figure 17) Kymography is an aid in differentiating aneurysms from mediastinal tumors because not all mediastinal tumors exhibit movement. Furthermore, although many tumors may exhibit movement, it will not necessarily be aortic in origin. The pulmonary arteries or

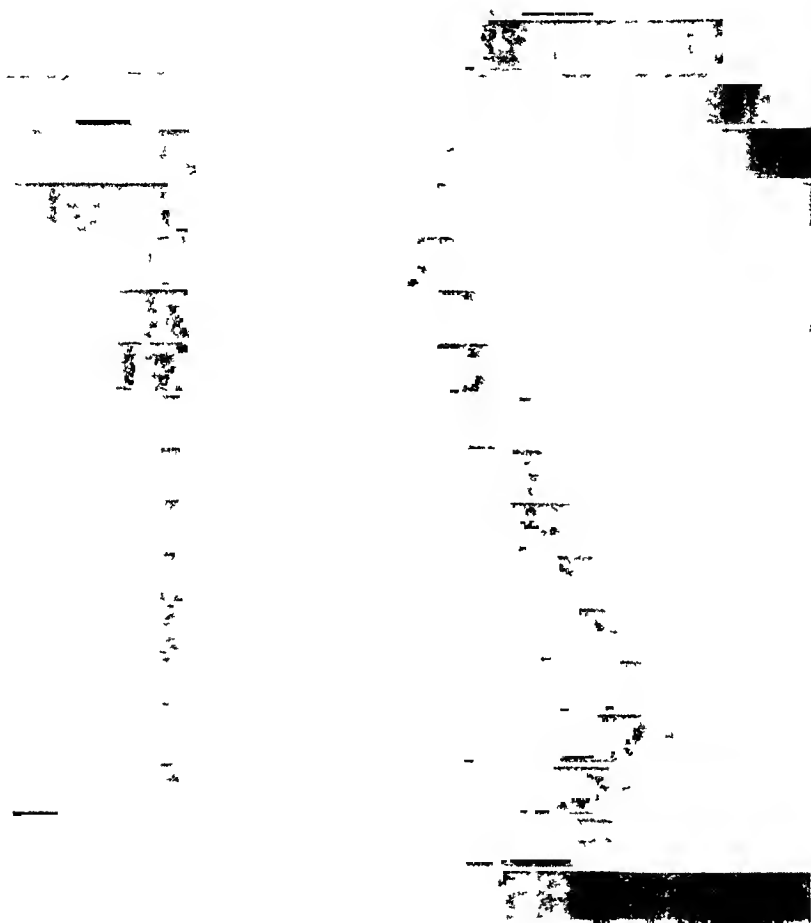


FIG 13 "The myxedema heart" The ventricular waves are low, slow moving, and have a small peak preceding systole

A 36-year-old colored woman who has been observed in the Out-Patient Department for two years. Her BMR has never been above — 20 per cent even following thyroid medication. B P 115/75. EKG showed evidence of myocardial damage.

ventricles may be responsible for transmitting the motion, and it will then bear pulmonic or ventricular waves. The kymograph can thus be of aid in diagnosing mediastinal tumors but cannot make the differentiation in all cases.

In our experience even early luetic aortitis produces a surprisingly characteristic kymogram (figure 18) The waves over the ascending aorta are prominent, increased in amplitude, retract slowly and simulate those of aneurysms The aortic waves on the descending aorta are unchanged In



FIG 14 Mitral stenosis and insufficiency In this case the waves are feeble and poorly defined, which are an indication of weakened musculature Patient was decompensated and had auricular fibrillation Note the truncated waves over lower heart border White male, aged 52, with history of rheumatic heart disease of 12 years' duration B P 105/70 (Courtesy Dr C Malone Stroud)

luetic aortitis there is a destruction of the elastic fibers in the media and a consequent loss of tone of the aortic wall which permits it to expand promptly and contract slowly This may allow a differentiation from arteriosclerotic changes

In hearts with hypertension the kymogram reveals no distinctive record

The amplitude of the aortic waves may be diminished, while those of the ventricle are increased (figure 19). Similar findings occur in arteriosclerotic heart disease and the aortic waves may be of average amplitude even in the presence of extensive calcification.

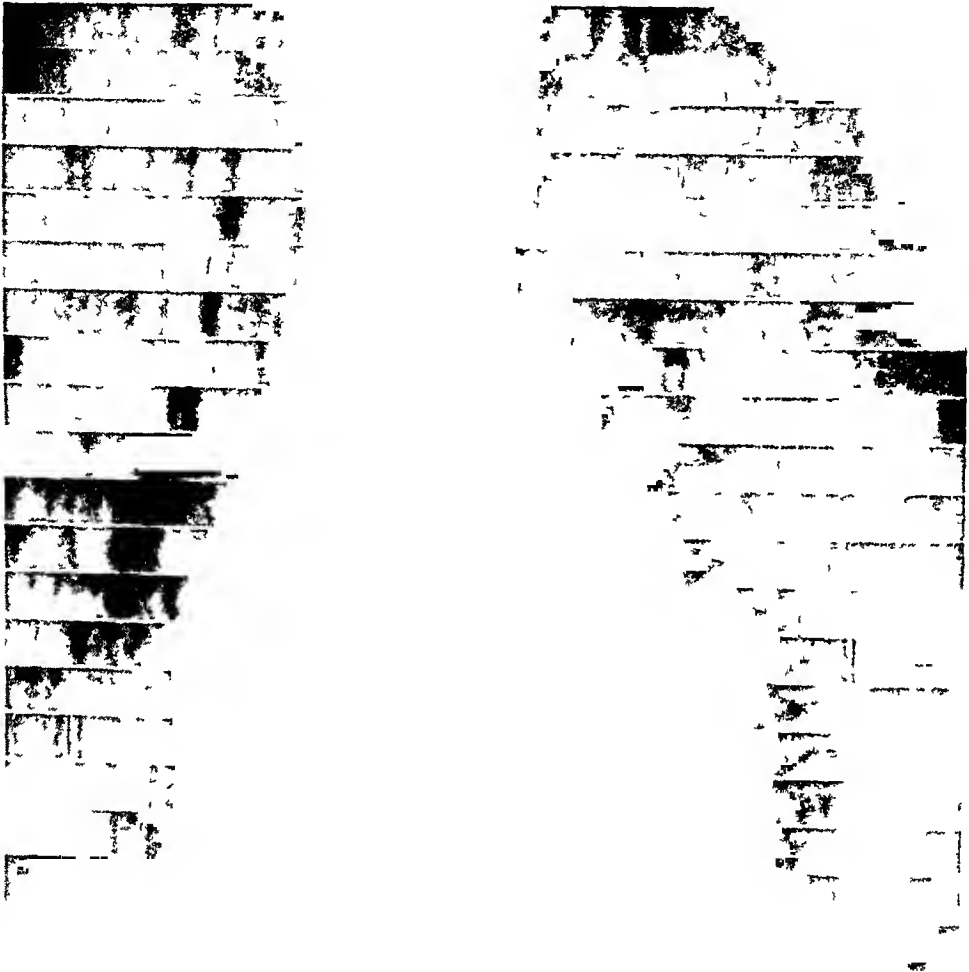


FIG 15 Aortic stenosis. Note that the normal horizontal line of aortic filling has become oblique, indicating a longer period of filling. Corresponding to this change is the prolonged phase of ventricular systole.

A 48-year-old white man who has had rheumatic heart disease for past 20 years. Signs of mitral stenosis and aortic stenosis present for past three years. B P 140/90.

Brednow and Deppe²⁰ in an excellent paper describe the changes produced in the kymogram with various arrhythmias. As yet we have been unable to study this problem but hope to do so in the near future.

Alterations in auricular waves are frequently seen on kymograms, but

their records are vague and usually complicated by the superimposed ventricular thrust. Until there is further improvement in the technic of reading and of making kymograms the auricular waves will remain difficult to interpret.

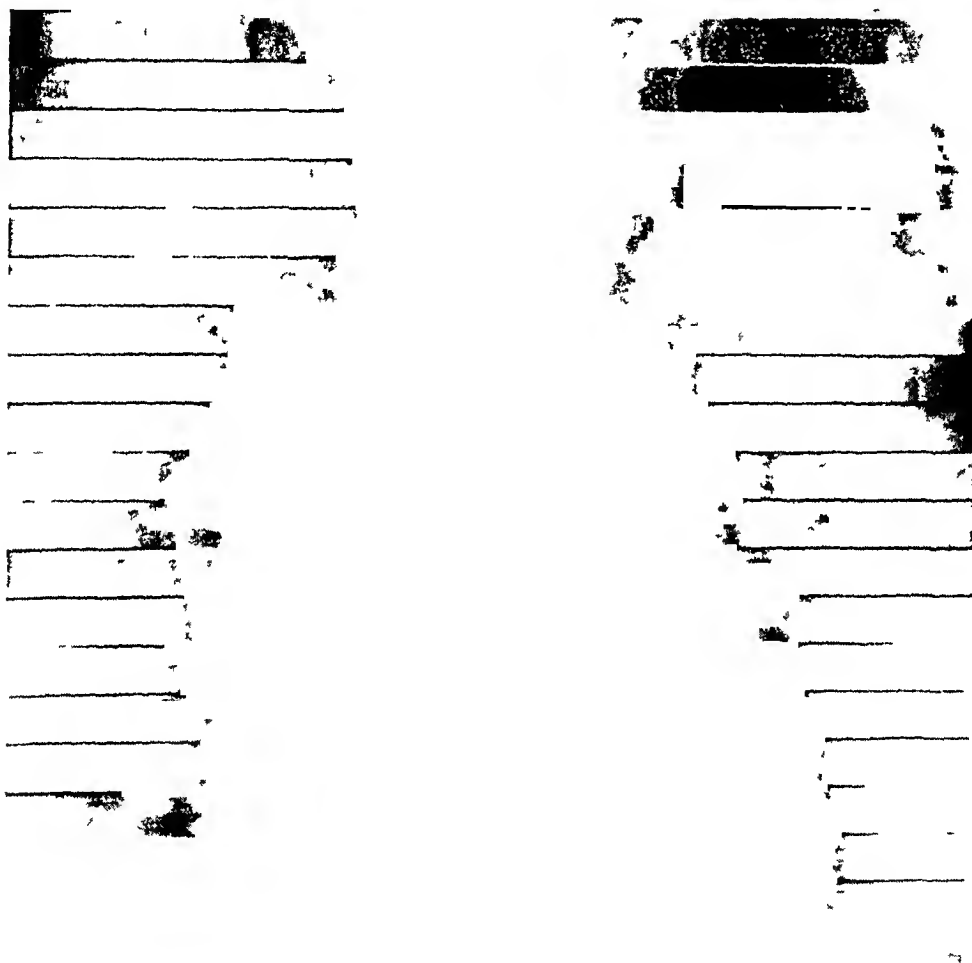


FIG 16 Aneurysm of ascending portion of aorta. Here the aortic waves are symmetrical, pyramidal in shape, and greatly increased in amplitude over ascending portion of arch. Aortic waves over descending aorta are not altered.

Colored man 45 years of age. Known luetic since 1932 with 4+ Wassermann test. B P 200/115.

The changes in the heart muscle which can be interpreted from the electrocardiogram as indicative of myocardial damage should presumably produce variations in the movements of the heart muscle which can be recorded on the kymogram. As yet we have been unable to identify clearly

specific changes, but feel that this problem offers a promising field for future investigation

SUMMARY AND CONCLUSIONS

1 Roentgenkymography permits a purely objective and accurate recording of the physiological movement displayed by an organ or structure

2 The procedure requires relatively simple and inexpensive apparatus. The cost of a kymogram is the same as that of the regular chest film



FIG 17 Aneurysm of descending portion of aorta. Even in the presence of calcification in the clot typical aortic waves are seen over borders of aneurysm. A 51-year-old colored man. Known luetic for 30 years. B P 136/76

3 The kymographic film is a permanent record which may be studied at leisure and compared with other records from time to time, as during the course of a disease

4 Kymography is an effort to fill the gap between roentgenoscopy and roentgenography and is not an attempt to replace either

5 Kymographic waves are the records of the form, amplitude, direction,

speed, frequency, and time relationships of movements occurring at equally spaced points on the border of an organ

6 The kymogram, as does the teleroentgenogram, portrays the size and outline of the heart, and in addition provides a record of the movement of

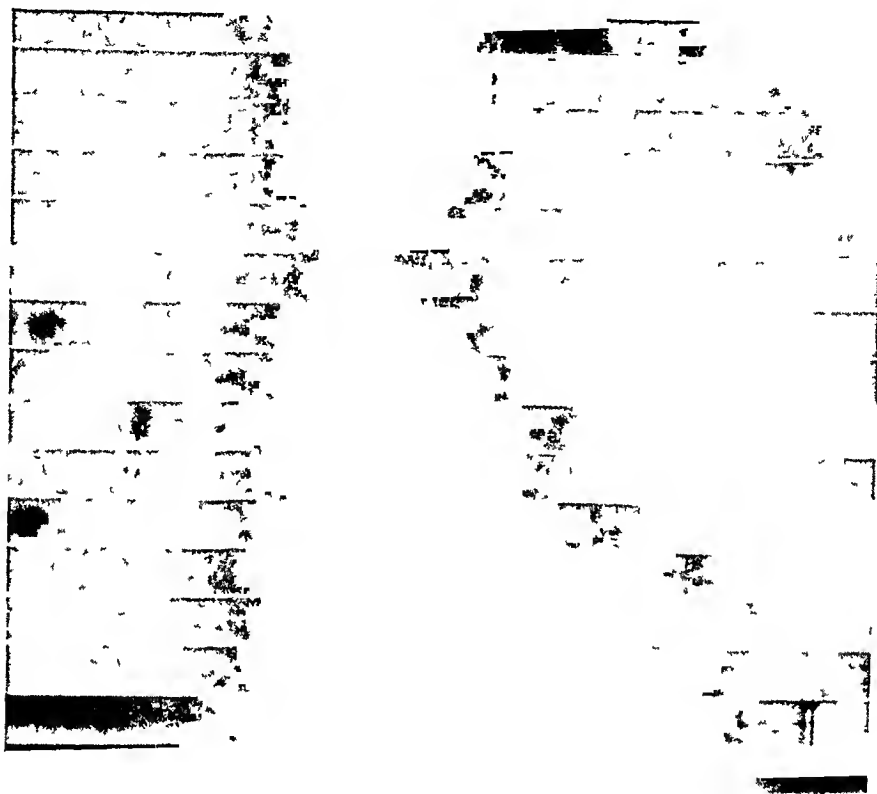


FIG 18 Luetic aortitis The waves over ascending aorta are prominent, increased in amplitude, and retract quickly These changes permit a differentiation between luetic aortitis and arteriosclerotic lesions

A 48-year-old colored widow who complained of precordial pain and palpitation of one year's duration B P 138/98 Faint systolic murmur heard over aortic area Wassermann test 4 +

the chambers of the heart, and information so obtained is frequently of clinical value

7 It permits a topographical identification of the heart chambers and great vessels

8 There are diagnostic kymographic tracings in certain types of heart disease, notably in aortic insufficiency, aortic stenosis, hyperthyroidism, myxedema, constrictive adhesive pericarditis, tuberculous pericarditis, pleuro-

pericardial-diaphragmatic adhesions, aneurysms of the ascending aorta, luetic aortitis, cardiac infarction, "nervous" or "irritable" hearts. With future research and the accumulation of data, the characteristics of other types of heart disease may be identified.

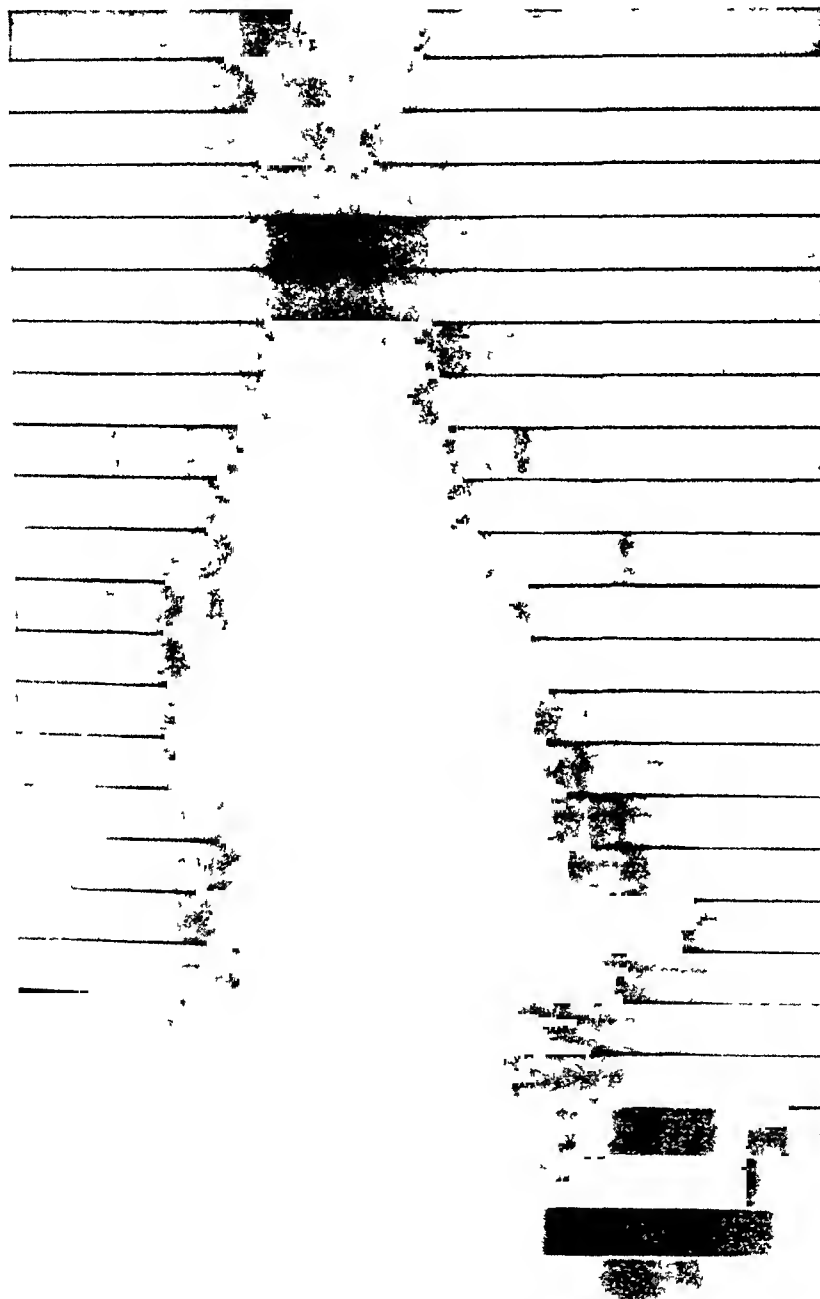


FIG 19 Essential hypertension. Note aortic waves are inconspicuous and ventricular waves of average amplitude.
Patient a young man 29 years of age with essential hypertension. B P remains constantly close to 220/110. No cardiac enlargement.

9 Kymography frequently proves of value in the differentiation of aneurysms and mediastinal tumors

10 The fund of information already gained on the physiology of movement has firmly established kymography as an important method in research

11 Kymography has been applied to the study of many structures exhibiting movement The results of our work in this field will be published shortly

The authors are indebted to Dr David P Barr, Dr Arthur Strauss, and Dr Hiram Liggett of the Department of Medicine, and to Dr Everts Graham and Dr J J Singer of the Surgical Department for permitting study of patients on their services Without their cooperation this work would not have been possible

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REVIVAL OF HUMAN HEARTS *

By WILLIAM B KOUNTZ, *St Louis, Missouri*

ATTEMPTS to develop a method which would make possible studies on the revived human heart have been made during the past six years. A number of references to such work may be found in the literature. The chief object of most of the observers has been to determine the viability of the organs, and the material has, with few exceptions,^{1,2} never been utilized for physiological study.

There are two excellent reasons why observations on the function of organs taken from the human body after death are of importance. One is that by this means the individual characteristics of the organs of man may be established. The span of life and the rate of physical development of man suggest that there is a basic difference between his organs and those of the usual laboratory animal, upon which most of the physiological observations are made. Again, it is a well known fact that characteristics of function differ to some degree in various species of animals. The differences in anatomical structure of the human body and those of laboratory animals may often lead to misinterpretation of results obtained in the physiological laboratory. A notable example of this is the work of Sir Thomas Lewis,³ who studied the nature of bundle branch block and localization of extrasystoles on the hearts of dogs. Because of the differences in anatomical structure of the mediastinum of the dog compared with that of man, Lewis's results were opposite to that obtained later in the human heart. The misinterpretation which resulted from the anatomical differences in the two animals led to a mistaken translation of the electrocardiogram for a period of 15 years.

A second reason that observations should be made on the function of organs taken from the human body after death is that many diseases which are not recognized by anatomical study may be understood. Man lives under circumstances entirely different from those surrounding most animals, which makes it impossible to reproduce the pathological lesions observed in man experimentally. The advent of biochemical studies in medicine has made possible the analysis of perfusing solutions, and thereby the study of functional pathology in far greater detail than heretofore. By such methods our knowledge of the relationship of individual organs to disease may be developed.

A technic for the revival of the human heart had first to be developed. The method of perfusion of the heart has not advanced since the days of Langdorff, who isolated a heart, inserted a cannula into the aorta, and per-

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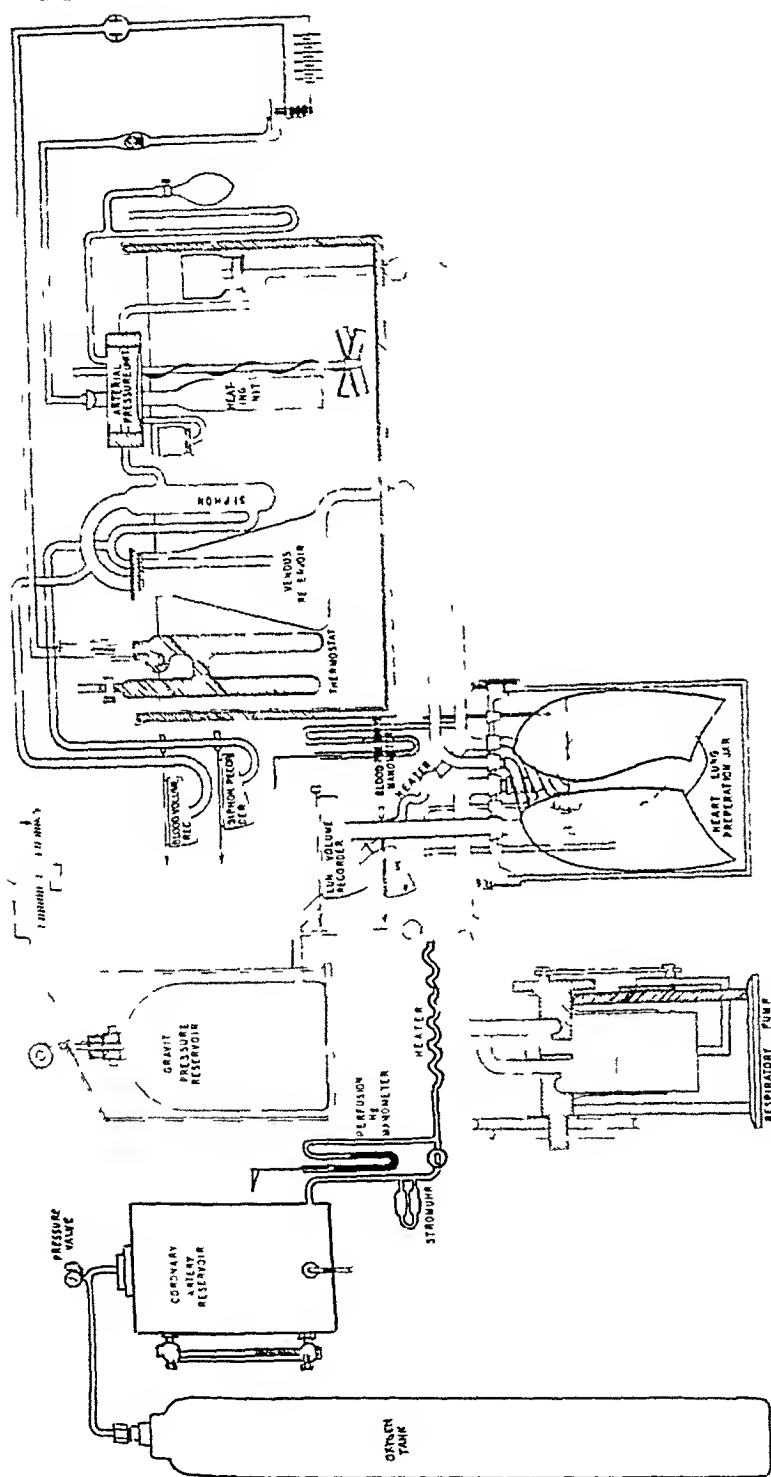


FIG 1 The outline drawing of the apparatus used for the work shows the Starling heart-lung apparatus with its arterial pressure unit. The gravity pressure reservoir which was attached to the cannulae in the ventricle and the pressure valve and coronary artery reservoir which was attached to the cannulae in the coronary artery system are present on the left of the drawing. A method for recording the size of the lungs, the volume of blood, and the rate of blood flow is noted. A respiratory pump to connect with the lungs is presented in the left hand corner of the drawing. Mercury manometers which record the perfusion pressures are attached to the perfusion systems.

fused the coronary vessels by backflow of the perfusing solution through the aorta. This method was satisfactory as a means of determining the viability of the heart but would not suffice to keep hearts viable for a period sufficiently long to permit physiological observation. Some exceptions to this were noted in the hearts of children. In general the hearts were found to dilate in a short period if the pressure in the aorta was raised sufficiently to permit perfusion of the coronary system. If low pressures were maintained the hearts revived imperfectly or not at all. For significant results a new method of perfusion was required. It was necessary to maintain a ventricular pressure in order to stretch the heart and permit it to contract. It was necessary also to perfuse the coronary artery at a pressure much higher than the ventricular muscle could withstand.

A cannula was constructed which would permit the development of different pressures in the ventricle and in the coronary arteries. Cannulae were inserted into the coronary arteries through the aorta. A large cannula was then introduced over the coronary ones through the aorta and past the aortic valves. Different pressures were maintained in the two systems by individual reservoirs.

The pressure in the cannulae of the coronary arteries was maintained at about 120 mm of mercury, whereas that in the ventricle was varied according to the contractility of the heart. By this method one could perfuse the hearts for a considerable period or could make heart-lung preparations which would last for several hours.

The hearts of 127 individuals who had died of various conditions have been studied. Sixty-five have been revived to the point of ventricular contraction. Of the 65, 48 developed regular cardiac mechanism and beat for a period of at least two hours. Fifteen heart lung preparations have been made and cardiac contractions against a blood pressure of 120 mm of mercury have been maintained for as long as four hours. The functions of the other hearts were studied by perfusion of the coronary vessels.

The time after death and the nature of the disease had definite influence upon the viability of the heart. It is a universal rule that the sooner the heart is obtained the more readily it revives. This is particularly true in individuals dying in good health and with heart disease. It is not so true of people with chronic illness. Since time after death was an important factor in revival, effort was always made to obtain the body as soon as possible. The actual time limit varied, however, from five minutes to six hours.

The causes of death were also varied and ranged from heart disease to death by accident. The age of individuals varied from still birth to an adult of 73. In general it could be said that in those cases dying from chronic illness revival could as a rule be accomplished more easily than in those succumbing to acute infection. The hearts of individuals who died of tuberculosis revived more easily than those of any other group whose death was due to a single cause. This applied not only to tuberculosis of

the lungs but also to generalized tuberculosis. The hearts of children were usually more responsive than those of adults. The greatest difficulty was encountered in the hearts of those who had succumbed to diseases of the heart itself. One exception to this rule was noted. Congenitally defective hearts in our experience were relatively easy to revive. Since the same result was observed in one case of emphysema in which chronic anoxemia had been a pronounced factor, it was thought that possibly decrease in

VIABILITY OF HEARTS

TIME	SUDDEN DEATH		NATURE OF ILLNESS							
			CHRONIC ILLNESS		ACUTE ILLNESS		HEART DISEASE			
	1	2	1	2	1	2	1	2	1	2
30 MIN	•••		••••	•	••••	••	••••	••••	••••	••••
1 HR	••	••••	••••	•	•••	••	•••	•••	•••	•••
2 HRS		•	••	•••	••••	••			••	••
3 HRS		•		•••	•••	••			•••	•••
4 HRS			•	•••		•••	•••	•••	•••	•••
5 HRS			••	••••		•••				
6 HRS.			••	••••		•				

1=HEARTS THAT WERE VIABLE •=ONE CASE
2=HEARTS NOT VIABLE

FIG 2 A chart which demonstrates the viability of hearts in 127 cases. The hearts of individuals dying of heart diseases are the least viable of all patients studied. Time after death is an important factor in reviving the hearts.

oxygen tension of the blood over a long period of time might be a circumstance favorable to revival. In general it was found that the longer the period after death the greater likelihood there was of thrombosis in blood vessels and the greater the probability of dilatation of the heart when the experiment was started.

A large number of problems has been studied in these hearts. The first consideration was the nature of bundle branch block. After the heart had been revived small incisions were made in the skin of the forearms and

left thigh through which small copper electrodes were introduced into the muscles of the extremities. The electrocardiograph was then attached to the body by the usual three leads and a normal record taken. The right or the left bundle branch was then cut and electrocardiographic tracings again made.

Section of the right bundle resulted in a curve which was not uniform in all experiments. The QRS complex was definitely prolonged to as much as 0.24 second. The initial deflection was down in Lead I and up in Lead III. In one instance we obtained a rather high deflection in Lead II, followed by inversion of the complex and T-wave. The character of the complex was varied by contact of the ventricle. Atypical curves were sometimes obtained when the heart was in an abnormal position or the contact to the body was through the left ventricle only.

When the left bundle was cut with the heart in normal position, curves were obtained in which the initial ventricular deflection was up in Lead I and down in Lead III. The curves were usually inverted in Lead II.

In addition to cutting the bundles the surface of the heart was electrically stimulated, and the localization and nature of extrasystoles determined.

Four general types of extrasystoles were observed. Concordant extrasystoles in which the initial ventricular deflection was upright in all three leads were obtained from stimulation of the conus of the right ventricle. Concordant extrasystoles in which the initial ventricular deflection was down in all three leads were obtained from stimulation of the region of the apex of the left ventricle. Discordant curves in which the initial ventricular deflection was up in Lead I and down in Lead III were obtained by stimulating the right ventricle everywhere except at the conus. Discordant curves in which the initial ventricular deflection was down in Lead I and up in Lead III were obtained from the left ventricle, except at the apex which covers a relatively greater area posteriorly than it does anteriorly. These results have substantiated the conclusions of Baker,⁴ whose observations were made on the human heart, and have been directly opposed to observations of Lewis on the dog's heart.

The nervous regulation of the heart was studied in subjects whose bodies were obtained immediately after death. The vagus and sympathetic nerves were isolated in the neck and stimulated by an electrical current. The results indicate that the action of the vagus and sympathetic nerves with a heart in normal mechanism was different from that previously supposed as far as the coronary flow was concerned. The vagus nerve when stimulated caused an increase in the coronary flow in these hearts instead of a decreased flow, as in the dog. The sympathetic nerve when stimulated decreased the flow through the coronary arteries in the experimental heart of man.

The coronary flow in the perfused beating heart and in the heart lung preparations made from the heart and lungs of these individuals is under consideration at the present time. The action of drugs which are com-

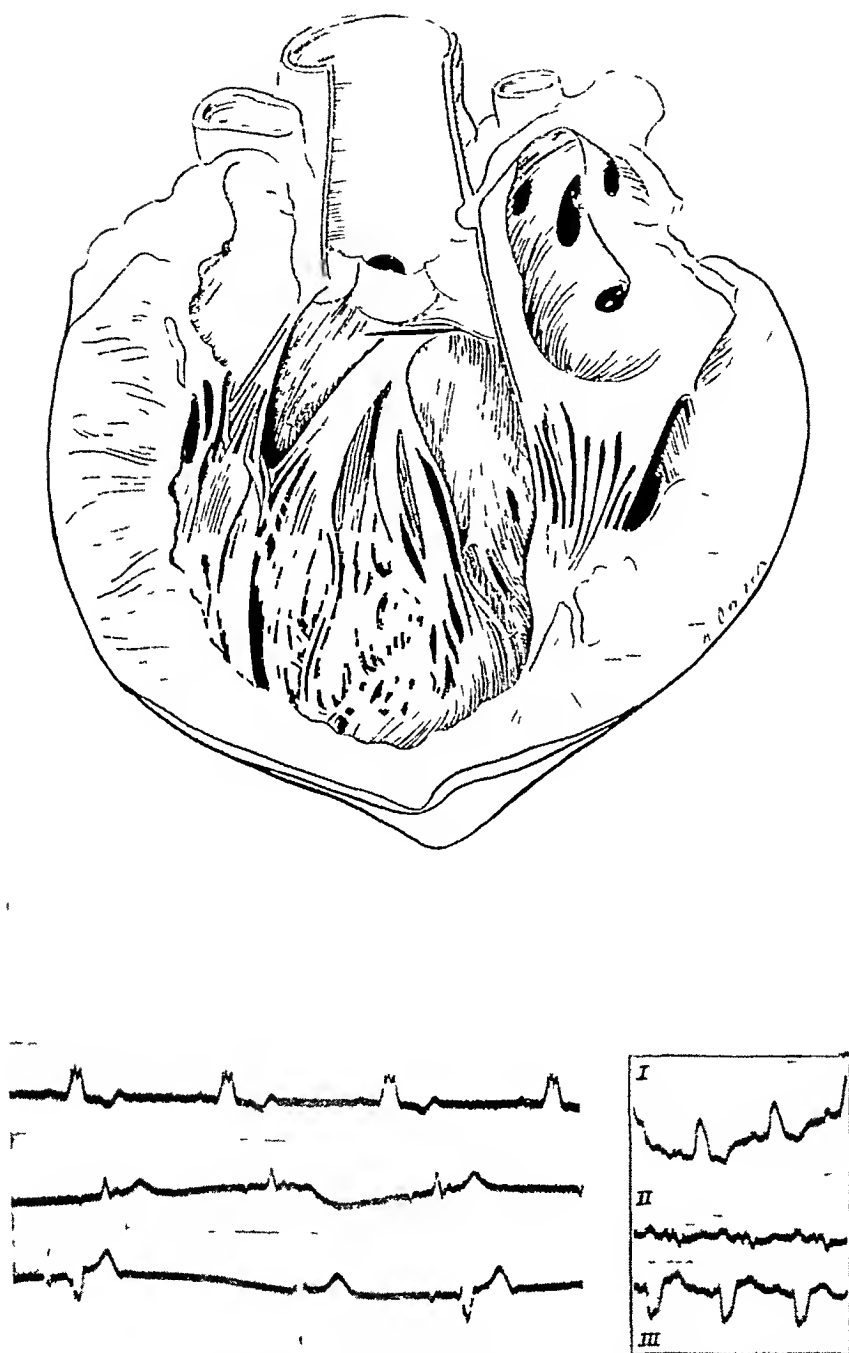


FIG 3 Drawing of a heart opened through the left ventricle showing an incision passing through the left bundle branch which produced curves resembling the common type of bundle branch block.

monly used in clinical medicine in the treatment of heart disease, and of others which are known to have a specific action, were studied by injecting them into the blood perfusing the coronary system of normal hearts. The hearts were then caused to dilate by cutting off the blood supply. After maximum dilatation of the heart was produced perfusion was started. It was found that the action of drugs was not the same in different states of diastolic volume of the heart. As a rule the drugs which decreased the coronary flow in the normal heart often increased the flow when the heart was dilated. The observation suggests that no single coronary dilator can be expected to act as such under all conditions. It emphasizes the clinical importance of studying the heart before a drug is given.

SUMMARY

A method is presented for revival of the human heart after death. This we believe establishes the possibility and the practicability of such a procedure. The results obtained from the study of the revived human heart indicate that information which may not be obtained from any other source is available from this procedure. We suggest that development of a branch of physiology and pathology based upon direct studies of isolated human organs would give us a far greater knowledge of deranged functions of organs in disease. It also might enable us to determine the basic physiology of many units of the body of which at present we know but little.

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LYMPHOSARCOMA AND HODGKIN'S DISEASE · CLINICAL CHARACTERISTICS '

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A COMPREHENSIVE survey of the available data reveals the following outstanding clinical characteristics of Hodgkin's disease

1 *Malignant and Protean Character of Hodgkin's Disease* Hodgkin's disease is a specific malignant disease which most frequently first manifests itself clinically by enlargement of the lymph glands and spleen accompanied by toxemia, anemia, wasting and cachexia. However, it is not confined to these lymphoid organs only. It is of historic interest to record that it was Hodgkin himself who was the first to make this observation, which has been repeatedly corroborated by numerous students of this disease. Indeed, more than half a century ago, in 1879, Gowers¹ in his comprehensive study of Hodgkin's disease gave details concerning the lesions not only in the lymph glands and spleen, but also in the skin, intermuscular tissues, bones, brain, soft palate, pharynx, tonsils, esophagus, stomach, small intestines, large intestine, liver, pancreas, peritoneum, thyroid, thymus, trachea, lungs, pleura, diaphragm, pericardium, heart muscle, suprarenals, kidneys, testes and ovaries. Further observations by numerous investigators have revealed that not a single organ or tissue has escaped invasion in Hodgkin's disease.

2 *Primary or Predominant Localizations of Hodgkin's Disease in Extra-Glandular Tissues* Hodgkin's disease is rarely, if ever, a uni-local or multi-local lymph-glandular disease. It is almost invariably a widely disseminated and protean disease showing marked variation not only in the duration, character and acuteness of its clinical course, but also in its predominant localization in different regions, tissues and organs in different individuals. Although, most frequently, enlarged lymph glands are the first lesion to attract clinical attention, numerous reports have appeared in the literature in which the primary or predominant clinical localizations of Hodgkin's disease appeared in the adrenals, appendix,³ bladder,⁴ bones,^{3, 4, 5, 6} bone marrow,⁸ brain,⁹ breast,¹⁰ bronchus, spinal cord, esophagus, eye, heart, intestines, kidneys, larynx, liver, lungs, nose, pancreas, peritoneum, pharynx, pituitary, pleura, prostate, salivary glands, skin, spleen, stomach, thymus, thyroid, tongue, tonsil, ureter and uterus.

3 *Presence of Toxemia in Hodgkin's Disease* Toxemia is an invariable accompaniment of Hodgkin's disease. As pointed out in a previous study,¹¹ specific hyperplasia of the reticulo-endothelial elements with or without lymphoid hyperplasia is only one phase and one stage in the pathology of Hodgkin's disease. There are now on record a great number of cases of

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this disease which ran an acute febrile course with toxic symptoms and then terminated fatally in from several weeks to several months. In these cases the fatal issue was caused primarily not by proliferative compressive phenomena, but by a severe toxemia which presented all the characteristics of an acute infectious disease. Although in the chronic forms, the toxic element does not always appear strikingly in the foreground, its unmistakable presence is clearly evidenced in the frequency of the recurring attacks of pyrexia, the progressive anemia and cachexia, the frequently demonstrable foci of necrosis in the specific lesions of the disease and in the parenchymatous degeneration of vital organs in which the specific lesions are absent.

4 *Lack of Pathognomonic Clinical Signs of Hodgkin's Disease* There are no characteristic or positively diagnostic clinical signs of Hodgkin's disease. Neither the character of the glandular enlargement, the blood picture, nor the temperature curve, singly or in combination, provides a conclusively diagnostic picture of Hodgkin's disease. A positive diagnosis can be made only on the basis of microscopic study*. This is easily accomplished by biopsy in accessible regions. The protean character of Hodgkin's disease and its primary clinical localization in internal organs and tissues in many cases may cause it to simulate a variety of local or systemic disorders and to present great difficulty in diagnosis. A biopsy may be unobtainable.

5 *Importance of Radiotherapeutic Diagnostic Test* In the absence of any biopsy there is one diagnostic test, however, which is considered exceedingly important to emphasize, namely, the radiotherapeutic diagnostic test. Since the appearance of the original articles of Pusey and Heinecke, the exceeding radiosensitiveness of both pathologic and normal lymphoid tissues to radium and roentgen-rays has become well known to all students of radiotherapy. The knowledge of this fact has at times been utilized by radiologists to determine whether a given tumor by its ready response to a given dose of radiation is of lymphatic constitution or origin. In Hodgkin's disease, before extensive fibrosis has occurred, the radiotherapeutic test can be of great help in causing a rapid and decided disappearance or diminution of the symptoms and objective signs of the disease.

6 *Unknown Etiology and Lack of Specific Therapy of Hodgkin's Disease* More than a century after Hodgkin's first description of the disease, its etiology still remains obscure, and a specific form of treatment has not been discovered. Chemotherapy and surgical intervention—with rare exceptions—have proved disappointing either as curative or palliative measures. The most efficient local treatment for Hodgkin's disease is universally recognized today to be the radium and the roentgen-ray treatment. The effect of both of these forms of radiant energy is prompt and efficient in influencing the cellular proliferative manifestations of this disease. Even bulky growths and infiltrations have been noted to disappear or regress promptly under radiotherapy, with great symptomatic relief not only of the compressive phenomena but also of the accompanying toxemia.

* Gordon's⁴³ biologic diagnostic test needs further study and confirmation.

7 Unfavorable Prognosis of Hodgkin's Disease Unfortunately, in spite of great improvement in radiotherapeutic technic, permanent cures have not been reported and, although prolongation of life for months and years has been noted by a number of observers, the fatal outcome has not been averted^{24, 25}

Similarity of Lymphosarcoma and Hodgkin's Disease The malignant characteristics of Hodgkin's disease and its close similarity to, if not identity with, lymphosarcoma have been repeatedly impressed upon me ever since I became interested in this problem many years ago. With the passing of the years the more closely and carefully I studied the literature and the personally observed cases the more firmly I became convinced that not only biologically but also clinically the two diseases in their course and manifestations are closely similar, if not identical. Whatever differences are observed at times may be regarded as mere variations of the same disease, which one would expect to encounter in different individuals with different tissue and organ susceptibility and resistance. It is this impression, which gradually has acquired the force of a conviction, that has induced me to review critically the recent literature and a series of 30 cases each of lymphosarcoma and Hodgkin's disease observed at Montefiore Hospital during the years 1922 to 1932.

CLINICAL CHARACTERISTICS OF LYMPHOSARCOMA AND HODGKIN'S DISEASE

Age In both groups of our series the greatest incidence occurred in persons past middle life, as occurs in epithelial cancerous growths. No striking differences were encountered in the age distribution between Hodgkin's disease and lymphosarcoma, as has been claimed by Kundrat and others. The youngest individual in our series was 11 years old. However, there are many reports in the literature of cases of lymphosarcoma and of Hodgkin's disease in children below 10 years of age. The important lesson to bear in mind is that both diseases are encountered most frequently during adult life but may occur at any age.

Sex In his original paper on lymphosarcoma Kundrat²⁶ stated that lymphosarcoma attacks males twice as frequently as females while Hodgkin's disease affects more frequently females. This statement, as was previously pointed out in a recent study, is not confirmed by the experience of other observers. In our series of cases of lymphosarcoma there were 13 females to 17 males, while in the Hodgkin's group there were as many males as females. Hence, whatever the ratio of sex incidence in a particular series of cases might be, it is of little or no significance in making a differential diagnosis between lymphosarcoma and Hodgkin's disease.

Organs and Tissues Involved in Lymphosarcoma and Hodgkin's Disease In our series the following tissues were found involved

Lymphosarcoma

Lymph glands, skin, subcutaneous tissues, muscle, breast, bones, dura, brain, pituitary, parotid, tongue, pharynx, tonsils, larynx, trachea, pleura, lungs, thyroid, thymus, vena cava, aorta, pericardium, heart muscle, stomach, spleen, liver, pancreas, jejunum, ileum, cecum, appendix, rectum, peritoneum, mesentery and omentum, adrenals, kidneys, ureters, prostate, bladder, seminal vesicles, spermatic cord, uterus, vagina

Hodgkin's Disease

Lymph glands, skin, subcutaneous tissues, breast, bones, dura, brain, pituitary, parotid, pharynx, bronchi, lungs, pleura, thyroid, vena cava, aorta, pericardium, heart muscle, thoracic duct, stomach, spleen, liver, pancreas, duodenum, jejunum, adrenals, kidneys, ovaries, uterus, bladder, vagina

A mere glance at the two lists reveals many more organs and tissues involved in lymphosarcoma than in Hodgkin's disease in the present series. To generalize from this series alone that lymphosarcoma has a tendency towards greater systemic dissemination than Hodgkin's disease is hardly warranted. If we but compare Kundrat's famous series of 50 cases of lymphosarcoma with Gowers' parallel series of 50 cases of Hodgkin's disease we shall detect but few differences.

Kundrat's 50 Cases of Lymphosarcoma

Lymph glands, skin, subcutaneous tissues, muscles, breasts, bones, dura, tongue, palate, pharynx, tonsils, larynx, trachea, bronchi, lungs, pleura, thyroid, thymus, pericardium, vena cava, esophagus, stomach, duodenum, jejunum, ileum, cecum, rectum, peritoneum, mesentery and omentum

Gowers' 50 Cases of Hodgkin's Disease

Lymph glands, skin, intermuscular tissues, bones, brain, soft palate, pharynx, tonsils, esophagus, stomach, small intestines, liver, pancreas, peritoneum, thyroid, thymus, trachea, lungs, pleura, diaphragm, pericardium, heart muscle, suprarenals, kidneys, testes and ovaries

However, neither in lymphosarcoma nor in Hodgkin's disease is the pathologic process limited to the organs and tissues enumerated above. In a previous study it was pointed out that it was repeatedly and conclusively demonstrated that not a single organ or tissue had escaped invasion in Hodgkin's disease. A comprehensive survey of the literature and our own observations have revealed that the same holds true for lymphosarcoma. Both diseases are protean in their manifestations. Clinically, both reveal the same marked variation in duration, character, course and selective localization in different regions, tissues and organs in different individuals. In lymphosarcoma as in Hodgkin's disease it is unquestionably true that in large series of cases the invasion of lymph glands is the first to attract clinical attention. Nevertheless, numerous reports have appeared in the literature in which the primary and predominant extra-glandular localization of lymphosarcoma occurred in the following organs and tissues: adrenal, antrum, appendix, bladder, bone, breast, brain (figure 1), spinal cord, esophagus, eye, heart, hemopoietic system, small intestines,^{28, 29, 30} large intestines,^{31, 32} lach-

lymphatic glands, larynx and trachea, liver, lung,^{33, 34} mastoid, mesentery and peritoneum, nasopharynx, neck and pharynx,³⁵ ovary, pancreas, pituitary,³⁶ prostate,³⁷ salivary glands, scrotum, skin,³⁸ spleen, stomach,³⁹ testes, thymus,⁴⁰ thyroid,⁴¹ tongue, tonsil,⁴² and vulva

The recognition that lymphosarcoma and Hodgkin's disease are protean in their manifestation and invade primarily and predominantly not only the lymph glands and spleen but also extra-glandular organs and tissues in different individuals, is of vast clinical importance. It stresses the need to remember that they masquerade under the semblance of a variety of non-malignant as well as malignant conditions, proper differentiation from



FIG 1 (Case 1) Lymphosarcoma or Hodgkin's disease of the brain (Courtesy of Dr C Davison, Neuropathologist, Montefiore Hospital)

which is of great importance from a diagnostic, therapeutic and prognostic standpoint. An early correct diagnosis of lymphosarcoma or of Hodgkin's disease is of vital importance, for in their early proliferative hyperplastic stage the lesions are more circumscribed and are highly sensitive to radium and roentgen therapy—the most efficient local therapeutic agents at our command today. In the later stages radiotherapy may fail because lymphosarcoma and Hodgkin's disease, even if checked in their further course, may have already produced irremediable damage either by marked invasion, compression or toxic degeneration of vital organs like the brain and cord, heart and lungs, liver or kidneys, or by ulceration and perforation of hollow viscera with secondary infection.

Compression Phenomena in Lymphosarcoma and Hodgkin's Disease

A review of the literature and personal observations have impressed me with the fact that invasive growth by direct extension or lymphatic permeation, and lymphogenous and hematogenous metastases play a more important rôle in the fatal issue of lymphosarcoma and of Hodgkin's disease than mere mechanical compression. Nevertheless, the presence and importance of compression in the advanced stages of the disease must be duly stressed. In our series of cases the involvement of organs by compression is shown below

<i>Lymphosarcoma</i>		<i>Hodgkin's Disease</i>	
1 Brain and cranial nerves	2 cases	1 Brain and cranial nerves	2 cases
2 Cord and nerve roots	3 cases	2 Cord	6 cases
3 Trachea	2 cases	3 Trachea	3 cases
4 Thoracic duct	1 case	4 Bronchi	1 case
5 Vena cava	1 case	5 Esophagus	4 cases
6 Ureters	3 cases	6 Left cervical sympathetic	1 case
		7 Thoracic duct	1 case
		8 Vena cava	1 case
		9 Intrathoracic veins	2 cases
		10 Aorta	1 case
		11 Heart	1 case
		12 Cystic and common duct	1 case
		13 Left renal vessels	1 case

While no sweeping deductions can be made from this small series of cases as to the relative frequency of compression in lymphosarcoma and Hodgkin's disease, nevertheless the observation that in the Hodgkin's group compression occurred twice as frequently as in the lymphosarcoma cases deserves attention.

Toxæmia in Lymphosarcoma and Hodgkin's Disease The following toxic or constitutional manifestations occurred in both groups of cases: weakness, anorexia, loss of weight, emaciation, brownish discoloration of skin, anemia, headache and fever. Marked febrile reaction occurred more frequently in the Hodgkin's group than in the lymphosarcoma cases. The Murchison-Pel-Ebstein relapsing type of fever occurred in only one of our entire group of 60 cases, a patient with Hodgkin's disease in the terminal stages. Evidence of necrotization of the lesions with secondary infection was frequently present in both series of cases but seemed to be more pronounced in the Hodgkin's group.

Is the cause of the febrile reaction—frequently more marked in Hodgkin's disease than in lymphosarcoma—due merely to cell necrotization with or without non-specific secondary infection, as believed by some students of this problem, or to be attributed to the presence of a filtrable virus as believed by Gordon,⁴³ Pullinger and others? A definite answer to these questions cannot be given in the present stage of our knowledge. Neither the tubercle bacillus—the most frequently incriminated organism—nor any other known

microorganism has been conclusively proved thus far to be the etiologic agent of lymphosarcoma or Hodgkin's disease

Relation of Tuberculosis to Lymphosarcoma and Hodgkin's Disease

The frequent presence of tuberculosis in Hodgkin's disease and its rarity in lymphosarcoma have been stressed by a number of observers. In our present series of cases pulmonary tuberculosis was found in two of our 30 cases of lymphosarcoma and in four cases of the Hodgkin's group. In the former the lesions consisted of a single calcified nodule in the right lung in one case and of active pulmonary tuberculosis in the other. In the four cases of Hodgkin's disease the findings were as follows: in case 1 the pulmonary lesions were healing and partially healed, in case 2 there was a healed tuberculous lesion in the right upper lobe, in case 3 there was a healed lesion in the right apex, in case 4—one of abdominal Hodgkin's disease with lumbar cord compression and no intrathoracic invasion—disseminated miliary tubercles were found in the lungs, liver and kidneys.

An analysis of the incidence of the type and extent of pulmonary tuberculosis in our group of cases of lymphosarcoma and Hodgkin's disease does not favor a tubercular etiology. Parenthetically, it is worthy of record that only six cases of pulmonary tuberculosis were found in this group of 60 cases of lymphosarcoma and Hodgkin's disease, encountered at Montefiore Hospital during the years 1922 to 1932, during which period nearly 4,000 cases of active pulmonary tuberculosis were observed clinically in this hospital and more than 600 studied at autopsy.

The Blood Picture in Lymphosarcoma and Hodgkin's Disease The presence of a diagnostic blood picture in Hodgkin's disease—secondary anemia, increased number of platelets, leukocytosis, increased number of polynuclear neutrophils, monocytosis, eosinophilia, and lymphopenia, has been stressed by a number of observers. Our own studies at Montefiore Hospital in the present group of cases did not reveal any essential difference between lymphosarcoma and Hodgkin's disease. A marked eosinophilia as high as 60 per cent was encountered in only one of our cases. The case, however, was diagnosed lymphosarcoma by several pathologists, and as Hodgkin's sarcoma and not lymphogranuloma by Dr. James Ewing. Hematologic study of our group of cases would therefore lead one to agree with the large group of observers who have failed to find a uniform diagnostic blood picture of Hodgkin's disease.

Course and Prognosis in Lymphosarcoma and Hodgkin's Disease The malignant character of lymphosarcoma and Hodgkin's disease has been recognized early in the course of their study. However, the impression still seems to prevail that Hodgkin's disease carries a better prognosis than lymphosarcoma. This is true to a very limited extent. Even if we omit from consideration the many acute cases of Hodgkin's disease reported in the literature in which fatal termination occurred within a few weeks or months from the time of clinical onset, a comparison of large series of cases shows that lymphosarcoma and Hodgkin's disease run a closely parallel race.

to the usual fatal issue. The average duration of either is between two and three years, although in either case at times extreme variations of from a few days to more than 20 years have been recorded (tables 1 and 2). The shortest duration of life in our Hodgkin's group was 2 months, the longest, 7½ years, the average, 2 years and 7 months. In the lymphosarcoma group the shortest duration of life was 6 months, the longest duration, 7 years, the average, 2 years and 1 month.

Mode of Death in Lymphosarcoma and Hodgkin's Disease In the past too much stress has been placed on the glandular invasion and enlargement and secondary compression in both lymphosarcoma and Hodgkin's disease, while the widespread invasion of the visceral organs either by direct extension from invaded lymph glands or by lymphogenous and hematogenous metastases has received insufficient emphasis. Moreover, in lymphosarcoma

TABLE I
Prognosis in Hodgkin's Disease

Author	No of Cases	Shortest Survival	Longest Survival	Average Survival	Remarks
1 Ziegler	70	1 month		1-2 yrs	50 per cent dead at the end of one year
2 Hodling and Brown	18	8 months	5 yrs		Treated by x-ray, radium, Coley's toxin
3 Wallhauser		2 weeks	6 "	2 "	Vast literature and personal observations
4 Coley	21	—	7 "		Only one 7-year survival
5 Billich	31	-1 year	7 "	2 3 "	
6 Yates and Bunting	63	1 month	8 "		Surgery, vaccines, x-ray treatment
7 Coley	39	—	8 "		Only one 8-year survival
8 Stone	164	—	8 "	2 7 "	
9 Craver	300	-6 months	9 5 yrs		32 patients, or 10 3 per cent, alive 5 years or over
10 Burnham	173	-1 month	10 "	4 25 yrs	Radium therapy
11 Dautwitz	56	-1 year	10 "	3 "	
12 Hummel	52	-1 "	10 "	3 4 "	
13 Evans and Leucutia	46		10 "	3 1 "	
14 Warthin	242	—	12 "	3 5 "	
15 McAlpin and Golden	42	7 months	12 "	2 7 "	
16 Blakeslie	1		13 "		
17 Goia	80	6 weeks	13 "	2 4 "	
18 Schreiner and Mattick	46	2 months	13 "		
19 Uddstromer	494	17 days	14 "		165 patients died in less than 1 yr, 464, or 94 per cent, in less than 5 years
20 Desjardins and Ford	133	-1 year	16 "		Only one 16-yr survival
21 Minot and Isaacs			17½ "		19 patients lived 6 years or more
22 Lerche	1		18 "		Surgery and irradiation
23 Fabian	205	3 months	18 "	2-3 "	
24 Gilbert and Babaianz	60		20½ "		17 patients well 6 4 years
25 Cunningham	25		25 "		One 25-yr survival

TABLE II
Prognosis in Lymphosarcoma

Author	No of Cases	Shortest Survival	Longest Survival	Average Survival	Remarks
1 Whitaker and Fisher	1	14 days			Lymphosarcoma of ileum with ulceration, perforation and peritonitis
2 Raiford	45	1 day	5 yrs		Gastrointestinal lymphosarcoma Six patients well 5 years after operation
3 Gunsett and Oberling	1		5 "		Inoperable lymphosarcoma of stomach with lymph node involvement, well 5 years after x-ray therapy
4 Luscher	13	-1 year	5 "		Only one 5-year survival
5 Garry	1		5 "		Well 5 years after excision of localized lymphosarcoma of left axilla
6 Liu	12	-1 "	7 "		
7 Berven	35	-1 "	8 "		Lymphosarcoma of tonsil Radium therapy Well after 5 years 36.7 per cent
8 Crowther	21	-1 "	8 "		Only one 8-year survival
9 Weeden	13	-1 "	8 "		
10 Desjardins and Ford	126	-1 "	10 "	2.4 yrs	
11 Leucutia	31	-1 "	10 "		
12 Spies	35	-1 "	10 "	1.3 "	
13 Coley	58	-1 "	10 "		Only six patients remained well 3 to 10 years under combined toxin and irradiation treatment
14 Simon	85	-1 "	11 "		
15 Burnham	—		12 "		
16 New	1		12 "		Inoperable lymphosarcoma of antrum Radium therapy Well 12 yrs later
17 Harper	1		13 "		13 yrs ago lymphosarcoma of neck excised No irradiation Four yrs later inoperable lymphosarcoma of cecum X-ray therapy Well for 9 yrs Then ulcerative lymphosarcoma of stomach Excision Recovery
18 Falta	1		13 "		Lymphosarcoma of stomach Resection and radium therapy Patient well 6 yrs and 9 months later
19 Rosenthal, Harris and Kean	10	-1 "	14 "		Follicular lymphoblastoma type
20 Ruppert	1		14 "		Patient well 14 yrs after total gastrectomy for lymphosarcoma of stomach
21 Hintz	34	-1 "	15 "		One 14-yr and one 15-yr survival
22 Kapel	1		15 "		
23 Minot and Isaacs			16 "		
24 Warthin	232		17 "	2-5 "	23 patients well 6 yrs or over
25 Coley		-1 "	22 "		

the toxic factor in the evolution and termination of the disease has been greatly underestimated. In our series of cases, although, as pointed out above, compression was present in 12 of the lymphosarcoma cases and in 25 of the Hodgkin's group, local compression played a predominant rôle in the immediate fatal issue in only 11 of the Hodgkin's cases and in 9 of the lymphosarcoma group. Toxemia and multiple visceral invasions were the most frequent cause of death in both diseases. Terminal pneumonia was a frequent ending.

MODE OF DEATH IN LYMPHOSARCOMA AND HODGKIN'S DISEASE

<i>Lymphosarcoma</i>		<i>Hodgkin's Disease</i>	
1 Tracheal compression	1 case	1 Tracheal compression	1 case
2 Esophageal compression	1 case	2 Compression of stomach, liver and bile ducts	1 case
3 Mediastinal compression	4 cases	3 Mediastinal compression	8 cases
4 Intestinal obstruction	1 case	4 Ureteral obstruction	1 case
5 Cord compression	2 cases	5 Cord compression	1 case
6 Toxemia and visceral invasion	19 cases	6 Toxemia and visceral invasion	18 cases

Differential Diagnosis of Lymphosarcoma and Hodgkin's Disease In a previous study on "Lymphosarcoma and Hodgkin's Disease: Biologic Characteristics" it was shown that none of the biologic diagnostic criteria described by Kundrat to differentiate lymphosarcoma from Hodgkin's disease have stood the test of careful investigation. The present clinical study further corroborates the same conclusion. Indeed, the more one studies this problem the more one becomes impressed that not only biologically but also clinically the two diseases are identical in their malignant manifestations*. Everyone with wide clinical experience with these two diseases knows how extremely difficult, if not impossible, it is to differentiate lymphosarcoma from Hodgkin's disease on mere clinical grounds in the absence of microscopic evidence. I have witnessed many instances in which expert clinicians and radiologists were unable to differentiate one from the other in the clinically most important group of cases—the mediastinal type—in which the aid of the roentgenologist is usually of great value not only from a diagnostic but also from a therapeutic standpoint in guiding proper irradiation therapy. Nor can the radiotherapeutic test—more prompt disappearance of the lesions in lymphosarcoma than in Hodgkin's disease under a similar dose of radium or roentgen-ray therapy—be always used as reliable guide in differential diagnosis. Highly cellular Hodgkin's disease in its early proliferative phase may be as sensitive or even more sensitive than late lymphosarcoma with secondary fibrotic changes.

Treatment of Lymphosarcoma and Hodgkin's Disease With very rare exceptions, chemotherapy, vaccine and toxin therapy have proved disappointing either as curative or palliative measures in either disease. Only in isolated lesions of the gastrointestinal tract has surgical treatment recorded some favorable results. As a whole, the most efficient local therapeutic agents are radium and the roentgen-rays. Although permanent cures have

* Gordon's biological differential diagnostic test requires further study and confirmation before it can be unequivocally accepted.

not been reported, moderate and, at times, marked palliation has been noted by numerous observers. Judged by final results, however, no sharp line of demarcation can be drawn between lymphosarcoma and Hodgkin's disease.

ILLUSTRATIVE CASE REPORTS

Case 1 Lymphosarcoma or Hodgkin's disease with primary symptoms of esophageal obstruction. C L, aged 53, had always enjoyed good health until the first week in October 1931, when he experienced difficulty in swallowing solid food. The difficulty became rapidly and progressively more marked. He vomited frequently and within the next six weeks lost 20 pounds in weight and considerably in strength. Medical examination including radiography and endoscopic examination of the esophagus resulted in a diagnosis of carcinoma of the esophagus. A biopsy taken from the constricted bulging area of the lower third of the esophagus was reported inflammatory tissue. However, so firmly impressed were the attending physicians with the primary cancerous nature of the esophageal lesion that another biopsy was done. This too failed to show any neoplastic growth.

On November 14, 1931, he was admitted to a large hospital in New York, with a diagnosis of carcinoma of the esophagus. He was emaciated and pale. The neck showed no enlarged lymph nodes, nor did any other regions of the body show any glandular enlargements. The chest and lungs were grossly negative. The heart was enlarged and a systolic murmur was heard at the apex. Abdominal examination was essentially negative. The liver and spleen were not enlarged. A blood count showed 4,980,000 red cells, 70 per cent hemoglobin, 10,000 white blood cells, 60 per cent polynuclears, 8 per cent band forms, 26 per cent lymphocytes, 6 per cent monocytes. Urinalysis was essentially negative. Radiographic examination of the chest showed "a dense homogeneous shadow extending out into the parenchyma from behind the left ventricle."

Diagnosis Lymphosarcoma of mediastinum with invasion of esophagus.

Course under roentgen-ray therapy and dilatation by bougies. Following dilatation of the esophagus by bougies and deep roentgen-ray therapy to the mediastinum very little relief of the obstructive symptoms was obtained. In the meanwhile the patient was rapidly developing symptoms of intracranial invasion evidenced by the appearance of headache, mental dullness, impaired vision, ocular palsies, nystagmus, papilledema, retinal hemorrhages and progressive narrowing of the visual fields. From the time of his admission to the hospital until the middle of December, a period of four weeks, he ran a fever reaching 101° F. Then a sharp rise occurred reaching 106° F. on December 20, 1931, the date of his death.

Antemortem Diagnosis Lymphosarcoma of mediastinum with invasion of esophagus and metastasis to the brain. (Figures 1 and 2)

Postmortem Diagnosis Lymphosarcoma of mediastinal lymph glands, both lungs, esophagus, stomach, peritoneum and brain.

Microscopic Examination Lymphosarcoma or Hodgkin's structure with lymphoblastic thrombi in vessels of tumor area in the lungs.

Comment The important clinical features deserving emphasis in this case are

1 The primary onset with symptoms of esophageal obstruction simulating primary cancer of the esophagus.

2 The absence of any peripheral lymph glandular enlargement during life and at necropsy.

*I am indebted to Dr. N. B. Selby, of New York, for the privilege of reporting this case.

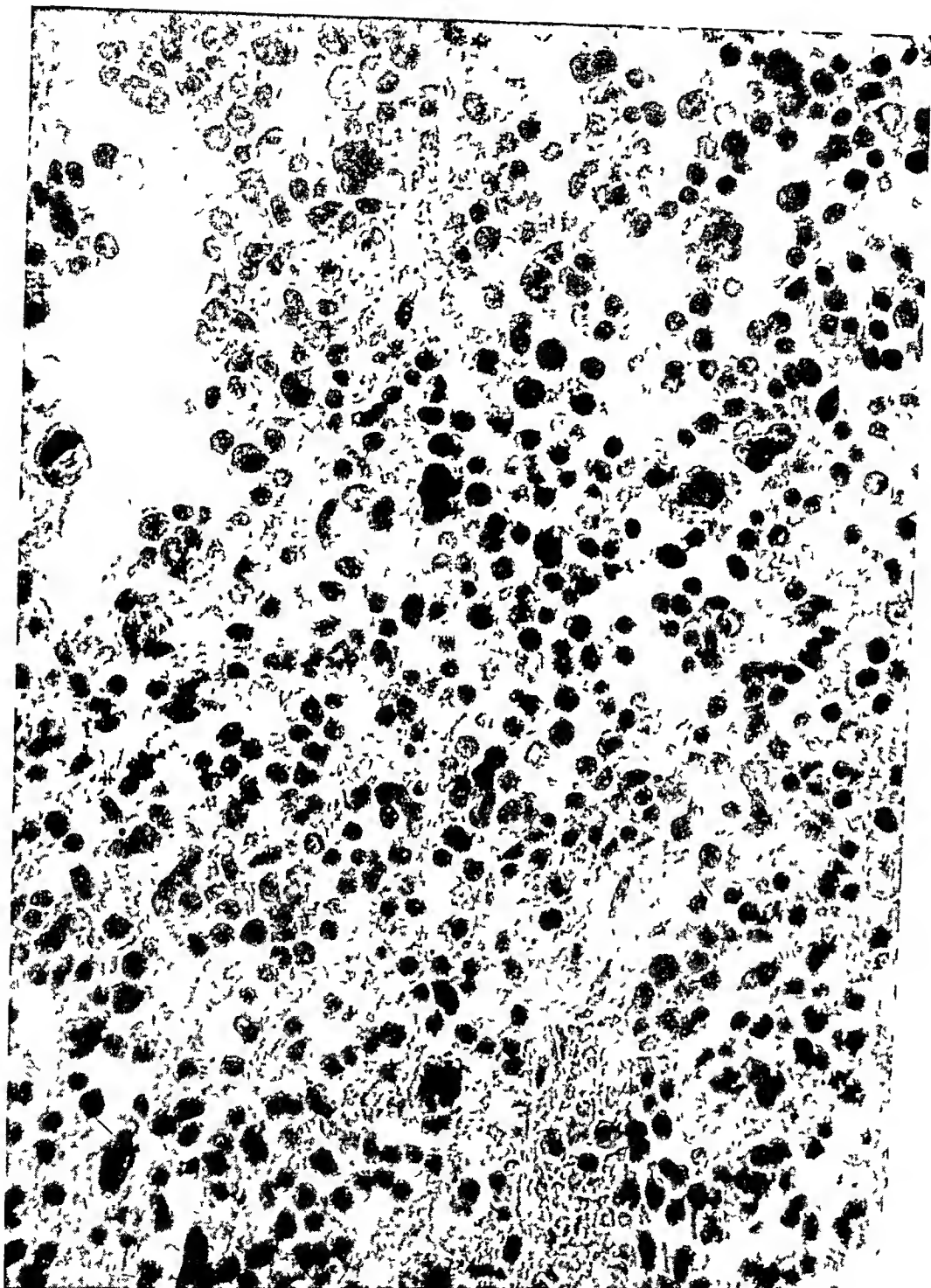


FIG 2 (Case 1) Microphotograph of lymphosarcoma or Hodgkin's disease of the brain
(Courtesy of Dr C Davison)

3 The silent development of a mediastinal lymphosarcoma until compression of the esophagus first called attention to the lesion

4 The extremely rapid course after the appearance of first symptoms—the total clinical duration of the illness being only 10 weeks

5 The invasion of the vessels of the lungs, and hematogenous metastasis to the brain

6 The extensive invasion of non-glandular organs

7 The limitations of roentgen-ray therapy in such widely disseminated lymphosarcomatosis or Hodgkin's disease

8 The lack of sharply demarcated morphologic criteria in "atypical" lymphoblastoma to differentiate lymphosarcoma from Hodgkin's disease
The postmortem specimens were studied by experienced pathologists who were unable to decide whether the case belonged to the lymphosarcoma or the Hodgkin's group

9 The absence of any predisposing or exciting causes for the development of the disease

Case 2 Lymphosarcoma with primary symptoms of pulmonary disease D S, aged 42, was admitted to Montefiore Hospital, September 25, 1924

Chief Complaints Dry cough, shortness of breath, pain in the right chest, marked weakness, loss of appetite and weight, swollen glands Duration of symptoms 17 months

He had always enjoyed good health until March 1923, when he gradually developed a dry cough, shortness of breath, loss of appetite and strength Three months later he was admitted to a hospital in New York where a diagnosis of pleurisy with effusion was made This was apparently confirmed by aspiration of clear fluid from the left chest At the end of five weeks of hospitalization and medical treatment he had lost 16 pounds in weight, had become weaker and his respiratory complaints were unrelieved He left the institution of his own accord and on the advice of his family physician betook himself to the country for climatic treatment There, within a period of five weeks he gained 19 pounds in weight, but his respiratory distress was not relieved and became aggravated by the development of pain in the right chest Greatly discouraged he returned to the city and again consulted his family physician who found an increase in pleural effusion and advised immediate hospitalization

In December 1923, he was admitted to a prominent hospital in New York where, in addition to the pleural effusion, enlarged lymph glands were discovered in the neck and axilla A biopsy of one of the nodes was diagnosed as lymphosarcoma Only then, nearly 10 months after the first onset of his respiratory symptoms, was deep roentgen therapy first given to his chest and the affected glands Temporary improvement occurred followed by relapse In March 1924, he was referred to a special hospital for the treatment of neoplastic diseases Examination at this time showed, in addition to intrathoracic involvement, enlargement of all the superficial lymph glands and marked deterioration of his general condition Under further roentgen-ray therapy there was slight improvement followed by relapse

On admission to Montefiore Hospital, September 25, 1924, he presented an advanced case of lymphosarcoma with predominant respiratory symptoms In spite of his long illness he was well nourished The skin of the extremities showed numerous excoriations the result of pruritus All the superficial lymph glands showed discrete and conglomerate enlargements The teeth were carious The tonsils were greatly enlarged and congested The superficial veins of the anterior chest were dilated

There were signs of fluid in both pleural cavities. The heart showed moderate acceleration and a loud systolic murmur at the apex. The pulmonic second sound was accentuated. The abdomen was distended, tense, and showed the presence of a fluid wave. The intra-abdominal organs could not be palpated due to the tenseness of the abdominal muscles. Rectal examination showed a distinct irregular enlargement of the prostate gland, the left lobe being harder and larger than the right. The penis, scrotum and lower extremities were edematous.

The patient steadily grew worse and on October 3, 1924, expired in a condition of pulmonary edema.

Antemortem Diagnosis

- 1 Lymphosarcoma of superficial, mediastinal and retroperitoneal lymph glands
- 2 Lymphosarcoma of lung and pleura, possibly of tonsils and prostate

Postmortem Diagnosis

- 1 Lymphosarcoma of the parotid, submaxillary, cervical, mediastinal, abdominal, iliac and inguinal lymph glands
- 2 Extraglandular lymphosarcoma involving the appendix, appendices epiploicae, bronchi, cecum, dura, kidneys, liver, lungs, omentum, pituitary (figure 3), parotid, prostate (figure 4), seminal vesicles, spinal nerves, submaxillary salivary gland, spleen, thymus, tongue, tonsils, ureters
- 3 Compression of thoracic and abdominal aorta, vena cava and pelvic veins
- 4 Bilateral hydroureter and hydronephrosis
- 5 Localized pleural effusion (right)
- 6 Pulmonary congestion and edema
- 7 Ascites and edema of lower extremities
- 8 Herpes zoster (healing), fourth and fifth thoracic levels (left)

Gross Characteristics of the Tumor "The tumor wherever found consisted of an elastic, more or less firm, grayish white, moist, smooth, homogeneous tissue found in discrete and conglomerate nodules or continuous sheets. In places were small areas of yellowish and hemorrhagic necrosis. The tumor in the posterior cervical region was in the form of palpably discrete nodules, which on dissection were found united by thin tumor strands. The growth enveloped the salivary glands, replaced the tonsils and lingual nodes, from the supraclavicular nodes it grew down in wide chains into the upper thoracic regions (and on the right side formed a mass about 10 cm. in diameter at the medial angle of the apex of the lung), it formed a complete envelope about the right lung and on the left side invaded the posterior regions of the pleural coverings. At the bifurcation of the trachea the tumor tissue enveloped but did not replace the anthracotic root glands, and finally in a continuous sheet it grew on the anterior and lateral surfaces of the bodies of the vertebrae from the base of the skull down to the coccyx, filled the pelvis and covered its lateral walls, surrounding in its course the aorta, ureters, nerve fibers and pelvic vessels and organs. In addition, the tumor had infiltrated extensively the omentum, the appendices epiploicae, surrounded the appendix and cecum and right surface of the thoracic dura. The glands in the root of the mesentery, around the celiac axis, axillary and inguinal nodes were replaced by tumor."

Microscopically the structure was that of reticulum cell lymphosarcoma.

Comment The important points deserving emphasis in this case are

- 1 The absence of any predisposing or exciting causes for the development of the disease
- 2 The primary clinical onset with signs of pleurisy with effusion persisting for several months before discovery of enlargement of superficial lymph glands
- 3 The loss of 10 months before a positive diagnosis of lymphosarcoma was made from a biopsy of one of the superficial lymph nodes

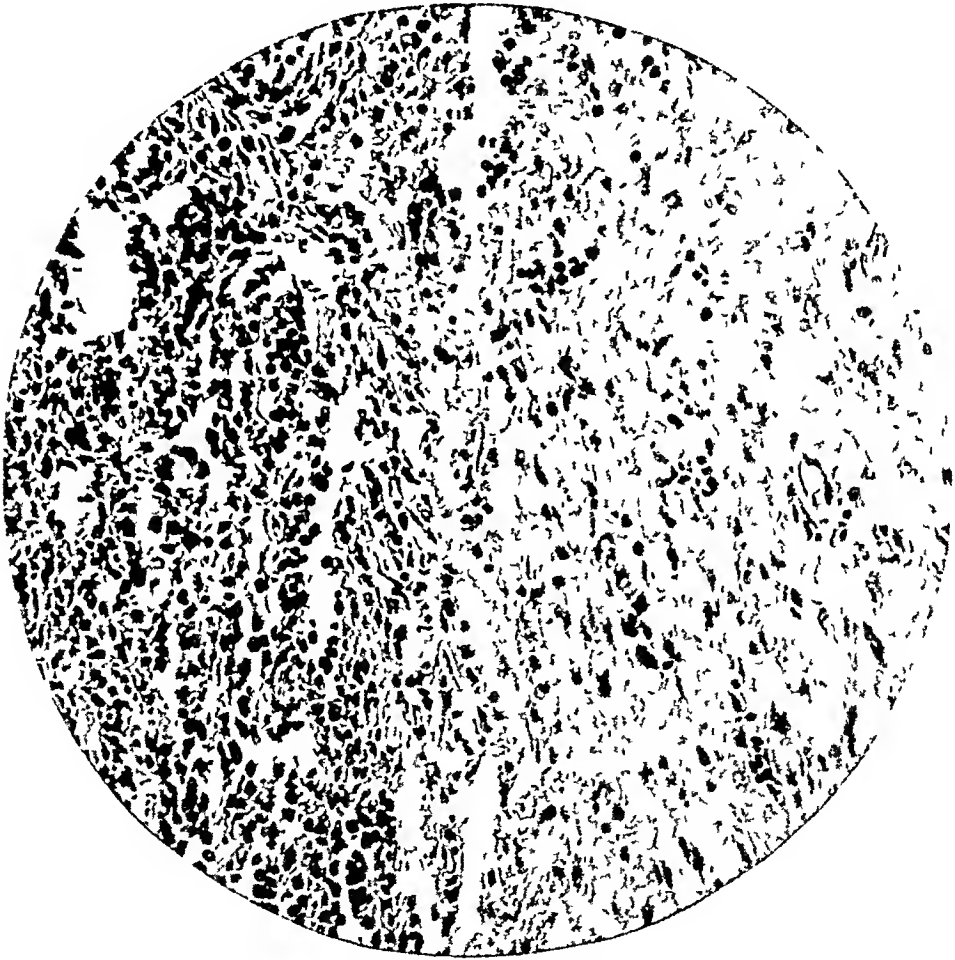


FIG 3 (Case 2) Lymphosarcoma of pituitary gland

- 4 The frequent presence of hemorrhagic necrosis in the neoplastic lesions
- 5 The accompanying toxemia
- 6 The apparent local resistance of advanced lymphosarcoma to roentgen therapy even in the hands of expert radiotherapists
- 7 The comparatively short duration of the illness (17 months) in a man who previously enjoyed good health

8 The pulmonary mode of death

9 The clinical recognition of lymphosarcomatous invasion of the superficial, mediastinal and abdominal lymph glands, pleura and lungs and the failure to recognize the apparently silent and extensive invasion of the pituitary, tonsils, tongue, thymus, thoracic dura, spleen, liver, kidneys, appendix, cecum, omentum, prostate, seminal vesicles and ureter

10 The compression of blood vessels, nerves and hollow viscera



FIG 4 (Case 2) Lymphosarcoma of prostate

Case 3 *Hodgkin's disease with primary localization in cervical lymph glands and secondary invasion of the base of the brain with generalization of the disease* Isidor D, aged 42, first came under observation of the Radiotherapy Department of Montefiore Hospital on July 14, 1930. His chief complaints were Painful swelling in right neck, pain in the right side of the head, face and neck, attacks of dizziness and unconsciousness, hoarseness, shortness of breath, weakness, and loss of 20 pounds in weight.

Some five years ago, in the summer of 1925, he noticed enlargement of the right cervical glands not accompanied by any local or constitutional symptoms. He paid

no heed to this enlargement until several months later, when its progressive growth finally made him consult a physician. He was promptly referred to the Skin and Cancer Hospital, New York City, where a biopsy of one of the lymph nodes was reported typical Hodgkin's disease. During November and December 1925, he was given a series of roentgen-ray treatments to the neck with good result. The swelling completely disappeared and he felt entirely well. Bearing in mind, however, the treacherous and malignant character of Hodgkin's disease, the patient was advised to report every two or three months for follow-up examination. He followed the advice and for the next three and a half years felt entirely well and failed to show any evidence of local recurrence or any other manifestations of Hodgkin's disease.

In the summer of 1929, he began to have attacks of severe neuralgic pain in the right side of the head, face and neck, without any evidence of local swelling. These attacks kept growing in frequency and severity and a few months later were accompanied by vertigo and loss of consciousness. In the fall of the same year, during one of these attacks of unconsciousness he fell to the ground and suffered a lacerated wound of the scalp which required several sutures. Shortly thereafter he was referred by his local physician to one of the large hospitals in New York where he was demonstrated by a member of the teaching staff before a large body of postgraduate students as a severe case of hemicrania induced by dental caries and was strongly urged to have eight of the incriminating teeth removed. Anxious to get relief, he promptly followed the advice. Unfortunately, relief failed to follow. Instead of diminishing, the attacks became more frequent and severe and were followed by rapid deterioration of his general condition.

On February 6, 1930, he was admitted to another hospital in New York for a swelling in the right tonsillar region. A biopsy of the swelling failed to reveal any neoplastic growth. Without any further clinical study and investigation of the paramount problem which was distressing the patient, namely, the severe headache and the attacks of unconsciousness, he was discharged from the hospital, unimproved, on February 21, 1930.

On April 10, 1930, he was admitted to Mount Sinai Hospital, New York. By this time his general condition had become greatly deteriorated. He felt very weak, was emaciated and cachectic and complained of excruciating pain in the right occipital and parietal regions requiring large doses of sedatives for its relief. The right side of the face and neck was swollen. The posterior pharyngeal wall bulged on the right side while the uvula was shifted to the left. There were no other glandular swellings found on clinical examination. Laryngoscopic examination showed possible right recurrent nerve paralysis. A blood count showed red blood cells 4,920,000, polynuclears 70 per cent, lymphocytes 26 per cent, mononuclears 4 per cent, eosinophiles 0. He was given a series of radium and roentgen-ray treatments to the right side of the head and neck and was discharged from the hospital on May 13, 1930, only slightly relieved from the attacks of severe pain in the head and the attacks of unconsciousness.

When first seen at Montefiore Hospital on July 14, 1930, his chief complaints were (1) Recurring attacks of pain in the right side of the head, face and neck accompanied by vertigo and loss of consciousness—one year's duration. (2) Hoarseness—one year's duration. (3) Shortness of breath—one year's duration. (4) Partial deafness and discharging right ear—six months' duration. (5) Swelling of the right side of the face and neck. (6) Swollen glands in the left side of the neck—one month's duration. (7) Loss in weight from 130 pounds to 105 pounds. Examination revealed a pale, emaciated, middle-aged man with swollen right cheek. The right eye, pupil and right palpebral fissure were smaller than the left (Horner's syndrome). There was nystagmus of the right eye both in a vertical and horizontal direction. There was ptosis of the right upper lid and right facial paraly-

sis The tongue was deviated to the right. The right half of the tongue showed atrophy and fibrillary twitchings. There was partial deafness of the right ear. The gums were spongy. The uvula was deviated to the right. The pharynx failed to show any swelling. The eyes showed clear media and normal fundi.

Neck Several moderately enlarged discrete lymph nodes were present in the right and left cervical regions.

Shoulders The right shoulder was lower than the left and drooping. There was atrophy of the right shoulder girdle with some winging of the scapula.

Face The right side of the face was swollen, but no tumor masses could be detected in the right cheek or parotid gland.

Chest and Lungs Negative on physical examination. Radiographically, slight thickening of the right apical pleura was noted, otherwise the lungs and mediastinum were negative.

Heart Moderate tachycardia, otherwise negative. Roentgen examination shows normal contours of heart and aorta.

Abdomen Liver, spleen, kidneys, lymph nodes are not palpable. No distention or ascites.

The axillary, inguinal and femoral lymph glands are not enlarged.

Blood examination Red blood cells 4,900,000, hemoglobin 70 per cent, white blood cells 13,000, polynuclears 70 per cent, lymphocytes 26 per cent, eosinophiles 4 per cent.

Urinalysis is essentially negative.

Diagnosis Hodgkin's disease with intracranial invasion and infiltration into the posterior jugular fossa with involvement of the seventh, ninth, tenth, eleventh and twelfth cranial nerves after their emergence from the medulla, causing pressure against the cerebellum or restiform body. Of interest is the absence of any signs or symptoms of intracranial pressure with a lesion of the magnitude of this one and located in the posterior fossa.

Course under Roentgen Therapy Following a course of deep roentgen-ray therapy given to the skull and neck through multiple portals, the patient began to show satisfactory improvement. On September 9, 1930, hardly more than a month after deep roentgen therapy was started, his headaches were almost entirely relieved and the attacks of vertigo and unconsciousness were no longer present. The deafness of the right ear was diminishing. The right Horner's syndrome was still present and a slight right facial paralysis persisted. The deviation, atrophy and fibrillary twitching of the right half of the tongue remained unchanged. The uvula was still slightly deviated to the right. The cervical and axillary lymph glands were barely palpable. Parallel with the local improvement his general condition improved and within the next two months his weight rose from 99 pounds to 110 pounds.

In February 1931, he began to have pain in the left upper abdomen. Examination revealed, for the first time since the onset of his illness, enlargement of the spleen. Under irradiation the enlargement promptly disappeared. However, the protean and treacherous character of Hodgkin's disease was once again revealed by invasion of the superior mediastinum. Under further irradiation this new invasion was again controlled. In May symptoms of mediastinal and pulmonary invasion recurred and the liver became enlarged. In June definite radiographic evidence of infiltration of upper half of left lung was noted. Under further irradiation he improved but promptly relapsed. In August it was evident that the fatal issue was close at hand. He had signs of generalization of the disease with pulmonary and intra-abdominal invasion. He gradually lost ground and died on December 2, 1931, with symptoms of toxemia and respiratory embarrassment. Necropsy could not be obtained.

Comment Among the many interesting clinical features presented by this case, the following deserve special emphasis:

1 The primary and solitary clinical localization in the right cervical region for several months before a positive diagnosis of typical Hodgkin's disease was made by biopsy

2 The prompt response and complete disappearance of Hodgkin's lesions in the early proliferative cellular phase of the disease before the onset of necrosis and secondary fibrosis

3 The long remission or slow silent development of the disease without any demonstrable physical signs

4 The invasion of the base of the brain either by infiltrative invasion or lymphatic permeation from the involved glands in the right cervical region

5 The mistaken diagnosis of hemicrania of dental origin in the absence of any glandular swellings or any other active signs of Hodgkin's disease

6 The loss of nearly one year before a diagnosis of intracranial invasion of Hodgkin's disease was made, at which time destructive or degenerative changes had already taken place in several cranial nerves

7 The slight response to moderate irradiation and the greater response to more intensive irradiation

8 The imperfect results from irradiation therapy in the late stages of Hodgkin's disease in general and in the nervous system in particular, when advanced irremediable degenerative changes make recovery no longer possible

9 The subsidence of toxic symptoms and gain in weight under irradiation even in late Hodgkin's disease of five years' duration

10 The generalization of the disease while under careful medical observation and radiotherapeutic treatment

11 The inadequacy of our most powerful local physical agents—radium and roentgen therapy—to cope curatively with the disease when generalization has occurred even though the palliative results and prolongation of life obtained in this case cannot be gainsaid

Case 4 Lymphosarcoma with bone metastases and intracranial invasion F B, aged 37, was referred to the Radiotherapy Department of Montefiore Hospital, April 17, 1930

Chief Complaints Aching and throbbing pain in the left fronto-temporal and lower occipital regions aggravated by pressure and posture, shortness of breath on slight exertion, and epigastric pressure

In 1916, at the age of 23, he noticed a small, painless lump in the right inguinal region, which remained apparently stationary in size for the next 11 years. In 1927, some three years ago, the lump began to grow progressively larger, producing pain on walking. One year later, in June 1928, an exploratory laparotomy revealed a large deep-seated ilio-lumbar mass which on pathological examination was reported as lymphosarcoma. One month later he was referred for radiotherapy to Dr Maurice Lenz, of New York. At this time examination revealed no other sites of invasion with the possible exception of the cervical and axillary nodes which were slightly enlarged. Following a series of high voltage roentgen treatments to the right ilio-lumbar, inguinal and femoral regions the pain and swelling disappeared and the patient felt completely relieved.

On April 17, 1930, he first came under observation at Montefiore Hospital. His

chief complaints were (1) Aching pain in the left fronto-temporal region—eight months' duration (2) Occasional throbbing pain in the lower occipital region aggravated by pressure and posture—three months' duration (3) Shortness of breath on slight exertion (4) Epigastric pressure—a few months' duration

He was in good general condition, well nourished and only slightly pale. In the left fronto-parietal region there was a large, hard, tender, bony swelling, which on radiographic examination was found to be due to an extensive area of bone destruction involving the frontal and parietal bones (figure 5)



FIG 5 (*Case 4*) Lymphosarcoma of skull

The tongue, pharynx, tonsils, neck, mediastinum and lungs failed to show any neoplastic invasion on physical and radiographic examination. There were a few soft, slightly enlarged lymph nodes in the left axilla, which gave the impression of being non-neoplastic in nature. Careful abdominal palpation failed to reveal any enlargement of lymph nodes or spleen. The liver, however, was greatly enlarged, its upper border being at the fifth intercostal space, the lower border extending 12 cm below the costal margin. The surface was smooth, the edge sharp. Nodules and irregularities could not be detected. A blood count showed a slight secondary anemia. White blood cells 12,800, polynuclears 89 per cent, lymphocytes 7 per cent, mononuclears 2 per cent, eosinophiles 2 per cent. Urinalysis was essentially negative.

Neurological examination showed bilateral choked disk, left greater than right, with marked pigmentation and colloid degeneration which was more extensive on the right. The findings were interpreted as indicating metastatic invasion of the brain with increased intracranial pressure.

Course under Roentgen Therapy Following a series of roentgen-ray treatments to his skull and liver, he showed a rapid and satisfactory response. As early as July 1930, reexamination of the eyegrounds showed normal fundi. However, a few days later he began to have pain in the right shoulder. Radiographic examination revealed an area of bone destruction in the upper end of the shaft of the right humerus with periosteal thickening along the inner border of the shaft. This lesion also readily yielded to irradiation. Toward the end of the same year he felt well enough to resume his former occupation as counterman.

In the summer of 1931 he developed enlargement of the cervical, axillary, epitrochlear and inguinal lymph glands. The spleen was palpable 2 cm below the costal margin. On May 27, 1931, he complained of pain in the left inguinal region. The next day radiographic examination of the pelvis revealed areas of destruction in the right pubic bone and areas of sclerosis in the left pubic bone. In October the liver again became enlarged and was palpable 5 cm below the costal margin. Cautious irradiations controlled the above lesions. In February 1932, he complained of pain in the left chest. Radiographic examination revealed partial consolidation of the left lower lobe with a small pleural effusion. Under irradiation the pulmonary lesion cleared up entirely within a few months. In January 1933, he developed a tender mass over the sternum. This likewise promptly disappeared under irradiation. Toward the end of April he had a recurrence of the left sided pulmonary invasion with pleural effusion, which again yielded to roentgen-ray treatment. Examination in July still found him in good general condition. In spite of extensive high voltage roentgen-ray therapy given over a period of three years, a complete blood count done on July 5, 1933 showed no change from the one on the date of admission in April 1930. The red blood cells were 3,870,000, the hemoglobin 75 per cent, the white blood cells 5,200, the polynuclears 69 per cent, the lymphocytes 25 per cent, mononuclears 5 per cent, eosinophiles 1 per cent.

In August 1933, he began to lose ground rapidly. The liver enlarged to about 10 cm below the costal margin. The invasion of the lung and pleura recurred in aggravated form. There were multiple areas of bone invasion. He grew pale and weak. His cardiac and respiratory embarrassment progressively increased and finally, toward December 1933, he passed into a condition of coma and died. A necropsy could not be obtained.

Comment The outstanding clinical characteristics of this case are

- 1 The presence of an apparently stationary enlargement of the right inguinal lymph glands for 11 years before they assumed a rapid and progressive growth and intra-abdominal invasion and extension.

- 2 The lapse of one year (or should we assume 12 years?) before laparotomy revealed an extensive intra-abdominal lymphosarcomatosis continuous with the inguinal invasion.

- 3 The rapid response of long-standing extensive intra-abdominal lymphosarcomatosis to high-voltage roentgen-ray therapy.

- 4 The apparently hematogenous route of metastases as evidenced by the invasion of the skull—and later other bones—without any demonstrable glandular or other soft tissue lesions in the vicinity.

- 5 The generalized yet discrete invasion of organs and tissues.

6 The order of clinical progression (a) inguinal nodes, (b) lumbar nodes, (c) skull, (d) cranial cavity, (e) brain, (f) liver, (g) right humerus, (h) left humerus, (i) axillary lymph nodes, (j) pubic bones, (k) spleen, (l) epitrochlear lymph nodes, (m) lung and pleura, (n) sternum and ribs

7 The comparatively slight toxic or constitutional symptoms until a few months before the end in spite of many years of widespread lymphosarcomatous lesions which were actively treated by roentgen-rays. The blood examination in July 1933, showing apparently no changes within a period of three years of repeated roentgen-ray therapy over bones, liver, lungs and lymph nodes, is one of the most instructive in clinical medicine. It shows that irradiation carefully controlled by clinical and blood studies may be administered for years without any demonstrable injury to the hemopoietic organs in a disease in which they are greatly exposed to injury.

8 The long duration—six to 17 years—of generalized lymphosarcomatosis in rare cases.

9 The continued spread and generalization of the disease under very careful clinical observation and treatment with roentgen-rays stresses the important fact that no local mode of treatment in lymphosarcoma can be permanently curative when the disease becomes generalized, although even then prolongation of life in comfort for several years may be achieved by judicious and efficient radiotherapy.

Case 5 Hodgkin's disease with skeletal invasion and pathologic fracture of the spine. M. G., aged 32, was admitted to Montefiore Hospital, July 8, 1927, with a diagnosis of Hodgkin's disease with pathologic fracture of the third lumbar vertebra.

In February 1924, without any apparent predisposing or exciting causes, he developed painless swellings in the neck which gave rise to no local or constitutional disturbance. Six months later he began to have substernal pain, cough and blood-streaked sputum. He made the round of several clinics and hospitals where he was treated medically with indifferent results. In the summer of 1926 his symptoms became more marked and, in addition, he suffered pain in the abdomen and across the lumbar spine. Frequently he felt nauseated and vomited. His appetite was gone and he lost weight progressively. In April 1927, he was admitted to a large hospital in New York where a diagnosis of Hodgkin's disease with pathologic fracture of the third lumbar vertebra was made. Examination of the blood at this time showed 2,000,000 red cells, 36 per cent hemoglobin, 5,600 white blood cells, 59 per cent polynuclears, 38 per cent lymphocytes, 3 per cent mononuclears. Following roentgen-ray therapy to his chest and spine there was very little improvement in symptoms and on July 8, 1927, he was transferred to Montefiore Hospital.

Examination revealed a very anemic, dyspneic, asthenic, jaundiced and cachectic individual. The cervical, axillary and inguinal lymph glands showed discrete and conglomerate enlargements. Dullness and crackling râles were present over the base of the right lung. There was a systolic murmur at the apex and a diastolic murmur at the base of the heart. The heart rate was moderately accelerated. The blood pressure was 90 systolic and 28 diastolic. The abdomen was distended and showed a fluid wave. The liver and spleen were moderately enlarged. The spine was tender from the second lumbar vertebra down to the coccyx. Over the fourth lumbar vertebra there was a tender bony swelling. The legs were edematous. A blood count on July 8, 1927 showed 1,900,000 red blood cells, 26 per cent hemoglobin, 3,800 white blood

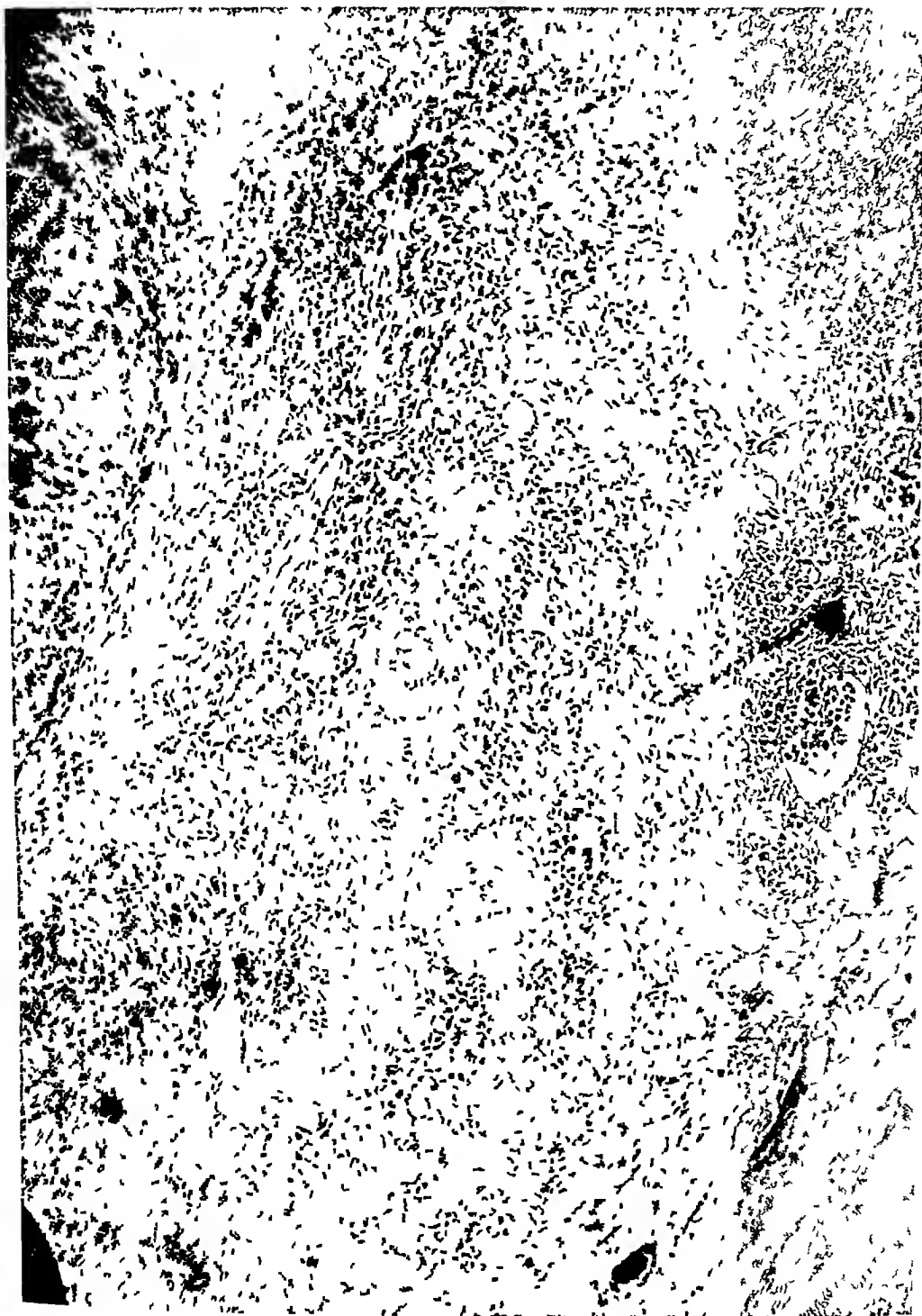


FIG 6 (Case 5) Invasion of adrenal, periadrenal tissues and blood vessels in Hodgkin's disease

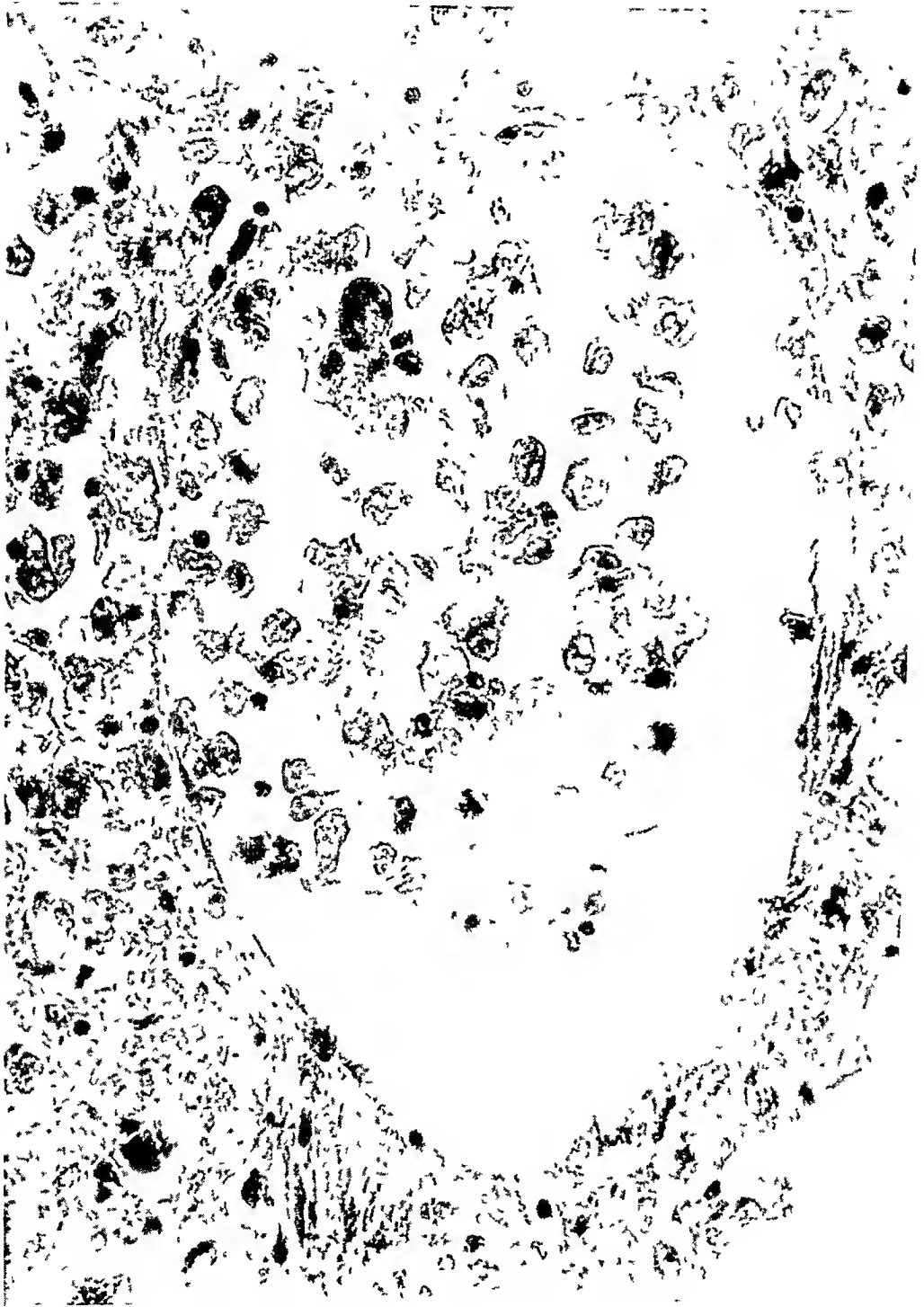


FIG 7 (Case 5) Higher magnification showing invasion of blood vessel in periadrenal tissues

cells, 68 per cent polynuclears, 29 per cent lymphocytes and no abnormal cells. Urinalysis gave a heavy trace of albumin and no other abnormal findings.

The patient steadily went down hill with symptoms of cardiac and respiratory embarrassment and died on August 19, 1927.

The antemortem clinical diagnosis was (1) Hodgkin's disease involving all the lymph glands of the body, (2) Hodgkin's disease of spleen, liver and spine.

Necropsy revealed (1) Hodgkin's disease of the superficial lymph glands and of bronchial and retroperitoneal nodes (2) Hodgkin's invasion of the spleen, head of the pancreas and left suprarenal gland (figures 6 and 7) and third lumbar vertebra (3) Aorta, vena cava and iliac vessels embedded in nodular masses (4) Infarction of spleen with moderate amyloid infiltration in places (5) Bronchopneumonia (6) Serofibrinous pleuritis, pericarditis and peritonitis (?) with effusion.

Microscopic examination Hodgkin's disease with few eosinophiles.

Comment The salient clinical features deserving emphasis are

- 1 The absence of any predisposing or exciting causes
- 2 The presence of painless and symptomless swellings in the neck for six months before the development of any evidence of intrathoracic invasion
- 3 The marked secondary anemia, the absence of eosinophiles and monocytes in the last blood examination
- 4 The presence of pain in the lumbar spine for many months before the discovery of the pathologic fracture of the third lumbar vertebra
- 5 The absence of any febrile stage during the patient's six weeks' stay at Montefiore Hospital
- 6 The poor response to radiation therapy of advanced Hodgkin's disease

Case 6 Primary lymphosarcoma of spleen with secondary paraplegia S I, aged 43, was admitted to Montefiore Hospital, December, 27, 1929, with paraplegia as the chief complaint.

In February 1928, he developed progressive weakness, occasional abdominal pain, anorexia, belching and loss in weight. Toward the end of 1928 epigastric pain after meals became so marked that he voluntarily began to restrict the intake of food. However, not until the summer of 1929 did he seek any medical aid. Finally on July 18, 1929, he was admitted to Bellevue Hospital where a large splenic tumor was removed. The pathological diagnosis was lymphosarcoma of spleen. The patient made a good post-operative recovery and was discharged from the hospital on August 18, 1929. A few days later he developed pain in the small of the back radiating down both lower extremities, and difficulty in walking. On September 19 he was readmitted to Bellevue Hospital in a very poor general condition. He was slightly jaundiced and appeared cachectic. Radiographic examinations failed to reveal any metastatic foci in the lungs or spine. A blood count done on September 16 showed 4,000,000 red blood cells, 75 per cent hemoglobin, 8,000 white blood cells, 60 per cent polynuclears, 22 per cent lymphocytes, 14 per cent transitionals, 2 per cent eosinophiles and 2 per cent basophiles. The blood Wassermann test was negative. Urinalysis was essentially negative.

His condition rapidly grew worse. He suffered continuously from pains in his back and legs and gradually grew weaker. In November definite paraplegia was noted. He was then transferred from Bellevue Hospital to Montefiore Hospital, where he was admitted on December 27, 1929, in a pitiable and helpless condition with paraplegia and decubitus ulcers. He was emaciated and jaundiced. The peripheral lymph glands were not enlarged. The chest and lungs were negative on physical and

radiographic examination The heart was not enlarged, the rate regular, 72 per minute. The liver was palpable 1 cm below the costal margin. There were no intra-abdominal masses and ascites was not present. Both lower extremities were completely paralyzed. Neurological consultation elicited a diagnosis of lymphosarcomatous metastatic invasion of the cauda equina possibly by extension from the spine, and deep roentgen-ray therapy was suggested. On January 6, 1930, radiographic examination of the skeleton failed to show any vertebral involvement. There was evidence of an old fracture of the ninth and tenth left ribs. There was an area of bone destruction in the lower end of the right ilium. There was a fracture through the upper end of the shaft and lesser trochanter of the left femur.

Course under Roentgen Therapy Following two erythema doses of deep roentgen therapy over the lumbo-sacral spine there was some diminution of the pain in the back and some improvement in the paralysis of the lower extremities. However, the patient gradually went down hill with symptoms of progressive asthenia and wasting and expired on May 29, 1930.

Necropsy revealed lymphosarcoma of retroperitoneal lymph glands and liver and active tuberculous lesions in the upper lobes of both lungs in which lymphosarcomatous lesions were absent. It is to be regretted that the brain and cord were not removed and sections of bone were not secured for pathologic examination.

Comment The salient clinical features of this case are

- 1 The primary clinical localization of lymphosarcoma in the spleen with secondary invasion of the retroperitoneal lymph nodes, cauda equina and liver

- 2 The failure of splenectomy 18 months after the onset of first clinical symptoms to affect the further course of the disease which was chiefly dominated by the invasion of the liver and cauda equina, with production of paraplegia, decubitus ulcers and toxemia

- 3 The marked wasting and cachexia of toxic origin

- 4 The associated tuberculosis of the lungs with no demonstrable foci of lymphosarcoma in the affected lungs and no tuberculosis in the lymphosarcomatous organs and structures

- 5 The failure of roentgen therapy to affect the late compressive phenomena of lymphosarcoma in nervous structures when irreparable degenerative changes have taken place

Case 7 Hodgkin's disease with primary and predominant broncho-pulmonary symptoms A H., aged 32, was admitted to Montefiore Hospital, June 28, 1928, with the following chief complaints: Cough and expectoration, shortness of breath, night sweats, poor appetite, loss of weight and strength, pain in the upper abdomen and across the small of the back, swollen glands in the cervical, axillary and inguinal regions. Duration of symptoms one year.

Family History Negative

Previous History In 1917, ten years before the onset of his present illness, he developed an acute respiratory infection which was suspected to be tuberculous in origin. At the end of three months he made a good recovery and, with the exception of frequent head colds, had enjoyed good health until the onset of the present illness.

Present Illness In June 1927, he gradually developed cough, expectoration, shortness of breath, night sweats, loss of appetite and pain in the upper abdomen and across the small of the back. He lost weight rapidly and grew progressively

weaker One month later his family physician made a diagnosis of bronchitis and advised a stay in the country for a few weeks A few days after the medical consultation he noticed for the first time painless enlargement of the glands in the left side of the neck He left for the mountains and within a few weeks felt greatly relieved from his respiratory complaints and gained some weight and strength, but the swelling of the glands in the left side of the neck did not recede and the glands in the right side of the neck became enlarged However, the glandular enlargements gave rise to no local discomfort, and on return to the city in August 1927, he felt sufficiently improved to resume his occupation as garment worker Gradually his respiratory symptoms recurred in an aggravated form, and toward the end of December 1927 he was forced to discontinue his work

On January 28, 1928, he was admitted to a large hospital in New York where a radiographic study revealed a mass at the root of the right lung The cervical, axillary and inguinal glands and the spleen were moderately enlarged Several blood counts showed a slight secondary anemia The white blood cells varied from 6,400 to 3,700 per cu mm, polynuclears 75 to 90 per cent, eosinophiles 2 to 3 per cent, mononuclears 2 to 7 per cent, small lymphocytes 8 to 27 per cent

A biopsy of one of the cervical lymph nodes was diagnosed as atypical Hodgkin's disease

Following a series of roentgen-ray treatments to the left cervical, anterior mediastinal and left inguinal regions there occurred a diminution in size of the irradiated glands followed by an increase of weakness and abdominal and lumbar pain Slowly and progressively he lost ground His cough, expectoration and dyspnea increased His abdomen became more painful His ankles swelled and he became entirely bedridden

On admission to Montefiore Hospital on June 28, 1928, he was emaciated and cachectic The skin was darkly pigmented The parotid, cervical, axillary and inguinal lymph glands were moderately enlarged and matted together There were signs of a moderate pleural effusion on physical and radiographic examination The heart was not enlarged The rate was 135 per minute The blood pressure was 90 systolic and 60 diastolic The abdomen was tense and distended The liver and spleen were palpable 4 cm below the costal margin Both ankles were edematous

For the next four weeks he ran an irregular fever ranging between 98 and 104 His respiratory embarrassment increased Fluid developed in both pleural cavities His blood pressure sank to the low level of 66 systolic and 38 diastolic and on July 28, 1928, he died with symptoms of congestive heart failure

Necropsy revealed (1) Hodgkin's disease of the cervical, axillary, mediastinal, mesenteric and retroperitoneal glands (2) Hodgkin's invasion of spleen and lung (3) Compression of the thoracic duct with chylous ascites (4) Compression and obliteration of the cystic duct (5) Compression of the common duct (6) Compression of the left renal vessels with secondary atrophy of left kidney (figure 8)

Microscopically the lesions were typical of advanced Hodgkin's disease The lymph glands presented massive necrosis with complete replacement by fibrous tissue There were many endothelioid cells and a few Dorothy Reed giant cells but no eosinophiles

The spleen presented a necrotic mass in a fibrinous network at the periphery of which there were areas of hemorrhage and others of round cell fibroblastic infiltration with a few polynuclears and occasional endothelioid and erythrophage cells but no eosinophiles In one area the Hodgkin's cells infiltrated and partly formed the lining of a blood sinus

The left lung, in addition to a lesion of Hodgkin's disease, presented a large sharply demarcated infarct with areas of parenchymatous atrophy and replacement by loose fibrous tissue and necrosis and hemorrhage in the center

Comment The salient clinical features of this case are

- 1 The primary clinical onset with broncho-pulmonary symptoms persisting for several weeks before enlargement of glands in the neck
- 2 The delay of eight months before a diagnosis was made in a patient who was rapidly developing toxic and compressive Hodgkin's disease



FIG 8 (Case 7) Atrophy of left kidney due to compression of renal vessels by enlarged nodes of Hodgkin's disease

- 3 The poor response to roentgen therapy in late and severely toxic and necrotic Hodgkin's disease

4 The marked necrosis of spleen and lymph nodes, the severe toxemia, the irregular remittent fever and the marked hypotension without any evidence of Addison's disease

- 5 The compression of the thoracic duct with the production of chylous ascites

6 The compression of the cystic and common bile ducts with the production of hydrops of the gall-bladder and fatty degeneration of the liver

7 The compression of the left renal vessels with secondary atrophy of the kidney

8 The brief duration of the illness which was shorter by four months than in the preceding case of lymphosarcoma

9 The absence of tuberculosis or any other etiologic factor to account for the development of the disease and its rapid dissemination and short duration

Case 8 Primary lymphosarcoma of stomach A B, aged 55, was admitted to the hospital August 24, 1930, complaining of marked weakness, loss of weight, nausea, vomiting and a painful mass in the upper abdomen

In August 1928, without any apparent cause, he began to lose weight and strength. A few months later anorexia, nausea and occasionally vomiting made him consult a local physician. The diagnosis was doubtful and the remedies were ineffectual. In May 1929, he applied to a large hospital in New York, where his marked weakness and low blood pressure led to a diagnosis of Addison's disease and for a period of three months he was given adrenalin injections and other forms of medical treatment. He failed to improve and noticed in addition the gradual development of a painful mass in the upper abdomen.

In February 1930, he was admitted to another large hospital in New York in a markedly emaciated and cachectic condition. His skin was bronzed. There was a swelling in the nasopharynx and numerous small, hard nodes in the right supra-clavicular region. In the left upper quadrant of the abdomen and epigastrium was found a movable, firm, smooth, rounded mass which was non-tender and was thought to be either intragastric or intracolonic. A blood count showed a secondary anemia. The blood pressure was 80 systolic and 60 diastolic.

Roentgen studies of the gastrointestinal tract revealed evidence of either an intragastric or extragastric lesion. Gastrophotography suggested an intragastric lesion. No free hydrochloric acid was present in the stomach even after histamine. A diagnosis of gastric neoplasm, probably on the posterior wall, was then made.

A biopsy from a soft, white, large, glistening swelling involving the posterior pillars of the fauces was reported as showing a tumor of the Schminke type. In order to determine the local involvement of the naso-pharyngeal tumor, a roentgen-ray examination of the skull was made and was reported as showing findings in the sella turcica suggesting pituitary neoplasm. There were no neurological findings suggestive of this. The visual fields were normal.

Radiotherapy of the nasopharyngeal tumor caused a marked shrinkage and almost entire disappearance. Similar results were obtained with the abdominal tumor which shrank to one-fourth its former size. An operation upon the abdominal mass had been suggested both for diagnosis and treatment but the surgeons considered the patient a bad risk and so the radiotherapy was carried out.

The patient improved remarkably in strength and general well-being, and was discharged from the hospital. The final diagnosis was (1) Schminke tumor of nasopharynx (2) Pituitary neoplasm (3) Gastric neoplasm. Interrelationship of the three was not established.

He remained under observation and treatment at the radiotherapy department of the hospital until the summer of 1930, when he noticed two painless masses developing over the anterior chest. From this date his health began rapidly to decline and his symptoms recurred in aggravated form. On admission to Montefiore Hospital on August 24, 1930, he complained of weakness, loss of weight, nausea and vomiting,

pain and swelling in the upper abdomen and lumps in the chest. He was emaciated and cachectic. The skin showed a brownish pigmentation. He was toothless. The pharynx was congested but no masses were present. There were no enlarged glands in the neck. Over the second and third costo-chondral articulations were several small, hard, immovable masses apparently springing from the periosteum. In both axillae a few small, hard glands were present. The apices of both lungs gave a dull percussion note. The heart was rapid but otherwise negative on examination. In the upper abdomen an indefinite mass was felt. The liver and spleen were not palpable. Rectal examination revealed a hard, tender mass in the region of the prostate. A blood count showed red blood cells 4,150,000, hemoglobin 65 per cent, white blood cells 11,510, polynuclears 65 per cent, lymphocytes 32 per cent, undifferentiated cells 3 per cent. Urinalysis was essentially negative.

Radiographic studies. Chest. Apical thickening due to old tuberculosis and infiltrative mass in the region of the right upper lobe, extending out from the mediastinum a distance of about 1.5 inches. There is an extension from the hilum into the left upper lobe. A small pleural effusion is present at the left base.

Gastrointestinal Tract. Irregularity of the cardiac end of the stomach suggestive of malignant neoplasm. Barium enema of colon negative.

Skull. Sella turcica three times normal size. Thinning of floor and of posterior clinoid processes. Appearance is strongly suggestive of pituitary neoplasm.

Urinary Tract. Uroselectan test showed dilatation of pelvis and calices of right kidney. **Diagnosis.** Right hydronephrosis.

Analysis of the clinical and laboratory findings led to the following tentative diagnoses by different members of the attending and house staff: (1) Hodgkin's disease, (2) Hypernephroma with metastases, (3) Cancer of the bowel with metastases, (4) Cancer of the prostate with metastases.

On September 11, 1930, a biopsy of one of the nodes in the left axilla elicited the report: "All normal lymphatic structure is gone. The entire lymph node is replaced by closely packed round cells which infiltrate the capsule of the surrounding fat tissue. These cellular elements are uniformly small, the nuclei are fairly deeply staining. There is very little variation in the size of the cells. The nuclear elements are rich in chromatin. A vein outside of the lymph node is filled with a large number of lymphocytes. This is extremely suspicious of lymphatic leukemia" (Figure 9). However, a restudy of the blood showed 11,660 white blood cells, 74 per cent polynuclears, 20 per cent lymphocytes and 6 per cent undifferentiated cells.

The third week in September his respiratory symptoms became more marked and on the twenty-fifth of the month he died with symptoms of a terminal bronchopneumonia.

Necropsy revealed: (1) Lymphosarcoma of stomach with metastases to regional, retroperitoneal, periaortic, posterior and anterior mediastinal lymph glands, (2) Diffuse lymphosarcomatous invasion of entire peritoneum with hemorrhagic ascites, (3) Invasion of left spermatic cord, (4) Right hydronephrosis, (5) Invasion of thymic fat tissue, parietal pericardium, right lung and pleura, (6) Bronchopneumonia right lung, (7) Bilateral otitis media and mastoiditis, (8) Basophilic adenoma of pituitary.

Comment. Among the many interesting features presented by this case, the following deserve special emphasis:

1 The onset with gastrointestinal symptoms, marked asthenia and low blood pressure, which led to a mistaken diagnosis of Addison's disease.

2 The presence of a lymphosarcomatous tumor in the nasopharynx which morphologically presented the cellular structure of a Schminke tumor or lymphoepithelioma.

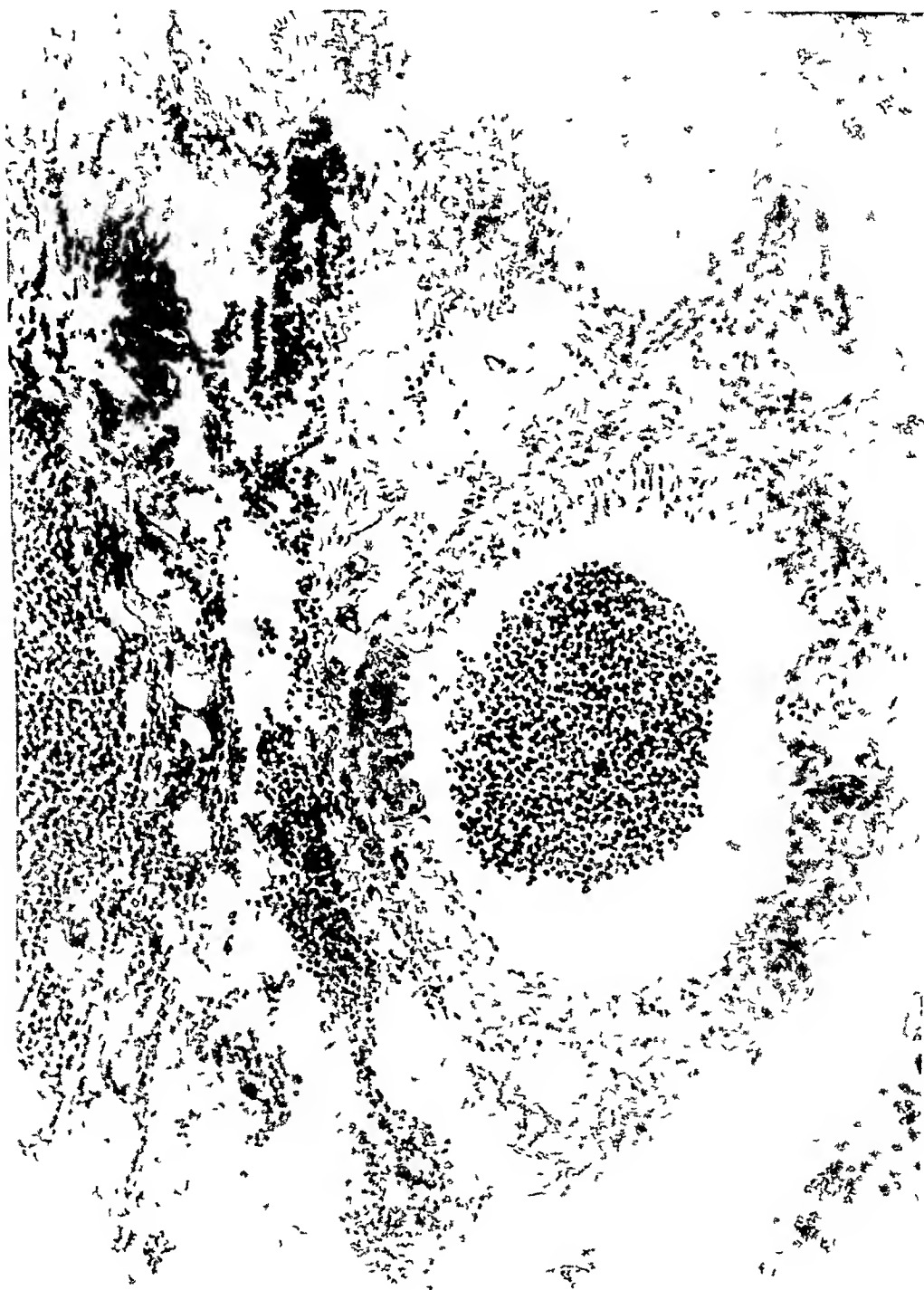


FIG 9 (Case 8) Invasion of capsule and blood vessel in lymphosarcoma of lymph node

3 The failure to recognize the lymphosarcomatous origin of, at least, some Schminke tumors led to failure to recognize the nature of the underlying abdominal tumor

4 The improvement that followed roentgen-ray therapy of the pharyngeal and abdominal tumors in a late case of generalized lymphosarcomatosis

5 The pleomorphism of lymphosarcoma in some cases The biopsy specimen from the nasopharynx was reported as lymphoepithelioma, while the one from the left axilla bore the characteristics of lymphatic leukemia Other areas from the intestines and the stomach gave the typical structure of reticulum cell lymphosarcoma and Hodgkin's disease

6 The extensive invasion of extra-glandular organs and tissues which dominated the clinical course of the disease

7 The toxic and pulmonary mode of death

Case 9 Lymphosarcoma of the transverse colon well four years after resection
B W, aged 57, was admitted to Montefiore Hospital, May 23, 1931, complaining of cramps in the abdomen, constipation and loss of 20 pounds of weight

He was in good health until October 1930, when he began to suffer from constipation, belching of gas, rumblings in the abdomen, loss of appetite and weight He consulted a local physician who diagnosed constipation and prescribed laxatives He failed to improve and in March 1931, applied to a large hospital in New York, where after two months of observation and treatment a diagnosis of a malignant neoplasm was made

On admission to Montefiore Hospital on May 23, 1931, he was well nourished There was no superficial lymph node enlargement The heart and lungs presented no abnormality on physical and radiographic examination The blood pressure was 144 systolic and 82 diastolic The abdomen was distended and tense In the region of the splenic flexure an oval movable mass was felt On radiographic examination obstruction at the splenic flexure was present with dilatation of the transverse colon A blood count showed 3,200,000 red blood cells, 55 per cent hemoglobin, 8,000 white blood cells A diagnosis of carcinoma of the splenic flexure was made and on June 22 1931, a resection of an ulcerated obstructive distal transverse colon was done The mesenteric glands were not enlarged and the liver was free from any invasion The pathologic examination of the removed tumor led to a diagnosis of lymphosarcoma The patient made a good recovery and has remained well until the present date Repeated clinical and roentgen examinations during the past four years have failed to show any evidence of lymphosarcomatous recurrence or invasion of any other organs and structures

Case 10 Lymphosarcoma of mediastinum well three years after irradiation
F R, aged 53, first came under observation at the Radiotherapy Department of Montefiore Hospital on May 23, 1931

The first week in April 1931, she first noticed enlargement of the left cervical lymph glands She would not have paid any attention to it, but she had headaches and spells of dizziness due to long-standing hypertension and therefore consulted her family physician He noticed the enlarged glands and had her chest roentgen-rayed Examination revealed enlarged bronchial glands A biopsy of one of the cervical glands was diagnosed as probable lymphosarcoma

When first examined at the Radiotherapy Department of Montefiore Hospital on May 23, 1932, she was well nourished and did not appear ill The teeth, tongue and throat were negative In the left supraclavicular region there was a tender mass measuring 6 by 6 cm, with a recent scar in the center It was firm in consistency and fixed to the underlying structures In the left axilla there was one enlarged lymph

node 3 by 3 cm in size and rubbery in consistency. There was upper mediastinal dullness. The lungs failed to show any gross abnormality. The heart was enlarged. The aortic second sound was accentuated. Blood pressure 165 systolic and 120 diastolic. There were no murmurs or acceleration. The abdomen was not distended. The spleen was not enlarged. The liver was palpable 3 cm below the costal margin. Vaginal examination revealed a fibroid uterus corresponding in size to a two months' pregnancy. Rectal examination was negative.

Laboratory Data Radiographic examination of the chest revealed a distinct enlargement of the superior mediastinum on both the right and left sides and the nodes at the right hilum showed marked enlargement. The appearance was most suggestive of Hodgkin's disease. A blood count on May 24, 1932 showed 4,750,000 red blood cells, 80 per cent hemoglobin, 9,500 white blood cells, 65 per cent polymorphonuclears, 29 per cent lymphocytes, 3 per cent each of eosinophiles and monocytes. Urinalysis was essentially negative.

Course under Radiation Therapy Following a series of high voltage roentgen-ray treatments to the mediastinum and cervical region the enlarged glands completely disappeared and have as yet shown no recurrence.

Comment The favorable results obtained in the last two cases of lymphosarcoma—in one by operation and in the other by roentgen-ray therapy—stress the fact that lymphosarcoma is not always from the outset a widely disseminated disease. It may for a time remain localized in one or a few organs or tissues. In such cases operation or irradiation may completely remove the local disease. A freedom from recurrence for three or four years must not lull us into an undue feeling of security as to permanent cure. Recurrence may take place. Hence we shall periodically carefully reexamine these patients and at the first signs of recurrence institute appropriate therapy. Until such time, however, we must be grateful for the excellent results now lasting three and four years respectively in definitely proved cases of lymphosarcoma, not differing clinically from many other similar cases which rapidly succumbed to the disease.

SUMMARY AND CONCLUSION

1 Lymphosarcoma and Hodgkin's disease most frequently manifest themselves clinically by invasion of lymph nodes and spleen. However, their malignant invasion is not confined to lymphoid organs and structures only. They are protean diseases and invade every organ and tissue of the human body.

2 Extra-glandular involvement by lymphosarcoma and Hodgkin's disease is not always an extension or a metastasis from primary invasion of lymph glands or spleen. Primary and predominant extra-glandular lymphosarcoma and Hodgkin's disease have been reported by numerous careful observers.

3 There are no pathognomonic clinical signs of lymphosarcoma and Hodgkin's disease. Hence, extra-glandular involvement of either disease has frequently been overlooked and mistaken for non-neoplastic conditions.

4 Both diseases are characterized not only by marked invasion, proliferation, replacement and compression of organs and tissues but also by necrotization, ulceration, toxemia, cachexia and febrile reaction.

5 A febrile reaction, especially of the relapsing type, has been more frequently observed in Hodgkin's disease but is by no means rare in lymphosarcoma

6 Both diseases may spontaneously run an acute, a subacute or a chronic course

7 There are no pathognomonic clinical signs by means of which Hodgkin's disease can be differentiated from lymphosarcoma. The only method of differentiation is on the basis of morphologic microscopic criteria, which are not always conclusive

8 Gordon's biological differential diagnostic test to differentiate Hodgkin's disease from lymphosarcoma necessitates the use of a biopsy and requires further study and confirmation before it can be unequivocally accepted

9 The etiology of lymphosarcoma and Hodgkin's disease still remains obscure. Gordon's claim for a filtrable virus as the cause of Hodgkin's disease still needs confirmation

10 There is no specific method of treatment for either disease. Chemotherapy, vaccine and toxin treatment, surgery and irradiation are purely palliative methods which, in selected cases, have produced favorable results with freedom from clinical evidence of disease for many months and years

11 Efficient and judicious radium and roentgen-ray therapy, always combined with skillful medical management, are the most important physical agents at our command today to cope with these two highly malignant diseases

12 To obtain favorable results in either disease by the methods available today, early diagnosis must be made before irremediable destruction or compression of organs occurs or before widespread metastases overwhelm the patient. Both lymphosarcoma and Hodgkin's disease invade, infiltrate and destroy organs and tissues not only by direct extension but also by lymphogenous and hematogenous metastases as in epithelial cancer. Hence, early recognition is absolutely essential for successful irradiation therapy or any other form of local treatment. Any delay of days or weeks, not to say months, is very hazardous

13 In doubtful cases where a biopsy is unobtainable, the radiotherapeutic test may be greatly helpful not only in arriving at a diagnosis but also in relieving the patient

14 The clinical course, the mode of death, the results of chemotherapy, vaccines, toxins, radium, roentgen-ray therapy and surgery as observed in lymphosarcoma and in Hodgkin's disease run very closely parallel. The prognosis in both diseases is similar

15 Hodgkin's disease varies in no fundamental clinical characteristics from lymphosarcoma. Whatever clinical variations it may present at times are merely variations that one may encounter in any disease affecting different individuals under different constitutional and environmental conditions

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THE PROPHYLACTIC AND THERAPEUTIC VALUE OF CONVALESCENT SERUMS IN SOME OF THE ACUTE INFECTIOUS DISEASES ~

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TODAY there is a steadily increasing interest in both the prophylactic and the therapeutic value of various convalescent serums. It is, however, extremely difficult to secure accurate information of the value of any agent in preventing acute infectious diseases. This is because of the many variables, having to do with the intimacy, degree and time of contact with an infectious individual, the degree and stage of infectivity of the patient, the relative resistance of the exposed individual, etc. Therefore, although the number of reports of well controlled prophylactic studies is increasing, the profession still views these efforts at prevention with some natural skepticism.

In the therapeutic use of convalescent serums in the acute exanthemata an analysis of the results can be more rigorous, but even here skepticism of physicians prevails. The reason for this attitude is probably not far to seek. The supply of convalescent serums has been meagre, except in a few places, and only a few large series of cases including the requisite controls have been published. Furthermore, in the usual infections of childhood, with which every doctor has had all too ample experience, each physician prefers to evaluate each prophylactic and therapeutic agent himself. Since convalescent serum has not been generally available, the profession has not been able to gain personal experience with its use. Even those who accepted the favorable conclusions of others, could not obtain convalescent serums in sufficient amounts for use in hospitals and private practice. In the regions where convalescent serums have been available, general practitioners and pediatricians are using these serums more and more, indicating in this way that they find them valuable.

It has been demonstrated at several convalescent serum centers that sufficient scarlet fever and measles serums can be obtained for widespread use in each center provided with a center. Each state could also supply its own needs by a comparatively simple expansion and by placing the centers in strategically situated cities.

The local departments of health have given their very necessary cooperation in Chicago, Milwaukee, Philadelphia, Providence, and recently in New York. The Detroit Department of Health deserves the credit of having established its own Convalescent Serum Center, this being the oldest large center in the United States. A number of European cities also have had similar organizations for years.

The relatively small fund needed for equipping and initiating each center is easily secured, even today. The donors furnishing serum receive com-

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pensation Only Wassermann and Kahn negative serums are used and the pooled serum is always passed through a Berkefeld filter before bottling The rigid technic and sterility tests of the U S Public Health Service are followed The serums retain their potency for at least 6 to 12 months, when kept at 4° Centigrade

Each center can become self-supporting by making a moderate charge for serum furnished for private patients, and at the same time provide municipal infectious disease hospitals with needed serum without cost These centers, with the cooperation of health departments, physicians and hospitals, can also investigate the possible value of convalescent serums for other infectious diseases, a field demanding immediate and intensive study

MEASLES CONVALESCENT SERUM

Although Cenci apparently was the first, in 1901 and 1906, to use convalescent serum for passive immunization, and reported favorable results in the few instances where it was used, it was not until 1918 that Nicolle and Conseil published their marked success in larger series of cases It is important to realize that Park and Zingher in this country, independently used the same method in the same year, although they did not publish their results until 1924 Many publications have followed, too many to quote here, especially as a number of excellent reviews are available* All have shown the definite value of passive immunization with convalescent serum and some of its limitations

In order to secure complete protection, the serum should be given intramuscularly within five days of exposure, and in a sufficient amount, that is one cubic centimeter for every year of age From 70 to 90 per cent complete protection is then secured The reason for this percentage difference undoubtedly lies in the variables already mentioned, as well as in the size and timing of dose Protection not infrequently occurs when serum is administered up to the eighth or ninth day after exposure, and though such effects cannot be relied on such a late attempt to obtain protection is advisable with debilitated or very young children With injections of serum between the fifth and eighth days, the result usually is attenuation to a mild or even insignificant attack, sometimes difficult to recognize, which apparently produces as lasting an immunity as the full blown disease Modified measles is rarely accompanied or followed by complications This limitation of the infection by delayed passive immunization may be the method of choice with exposed healthy children over five years of age However, everyone agrees that all debilitated children regardless of their age, and all children under five years, should be completely protected, if possible It is in these individuals that measles causes a high mortality because of complicating conditions, such as pneumonia, mastoiditis, etc Because of the benign nature of attenuated measles in an otherwise healthy child and because of the advantage of the

* For complete review of the literature through 1930, see Vol VII, of the Annals of the Pickett-Thomson Research Laboratory

permanent immunity conferred, an English observer has made a humorous suggestion with serious intent. He proposes giving "Measles teas," that is, inviting healthy children to have "tea" with a child during the infectious stage and later giving attenuating doses of convalescent serum between the fifth and eighth days or, better still, one-half the standard dose before the fifth day of exposure.

It goes without saying that in institutions such as hospitals, schools, orphan homes, etc., complete protection and not attenuation should be attempted. Usually a few attenuated or even complete attacks will occur even under these conditions, reexposing the others or newcomers. Since passive immunity persists for only about two weeks, individuals who cannot be removed from the infectious environment should be reinjected every two weeks during the period of exposure and every newcomer should receive serum. This procedure is innocuous, sensitivity not being caused by even repeated injections of homologous human serum, and, in our experience, reactions did not result from the use of properly prepared serum. In this way a hospital ward, for example, can be kept open continuously, and new patients admitted with almost negligible risk. Pooled adult normal serum will accomplish practically the same results as those just described, but it must be given in four times the amount. Pooled serum is more efficacious than serum or whole blood from one individual, such as a parent, because the pooling of many serums (usually 30) insures securing the immune principle which may be missing in a single serum.

Convalescent measles serum is potent when obtained as early as the tenth day after the beginning of the illness, provided the patient has been fever free for at least seven days. It is similarly potent when obtained as long as four months after recovery, and perhaps longer. The determination of how long a recovered individual will yield efficacious serum needs accurate determination. The longer the period, the larger can be the supply of serum, for each recovered adult or large adolescent can supply, with no risk, 250 c.c. of blood (yielding about 110 c.c. of serum) every two or three weeks for a period of six or eight months. In fact, their red blood corpuscles and hemoglobin usually increase, and polycythemia should be guarded against by blood counts before each bleeding.

It is generally stated that convalescent serum is of no avail after the actual development of measles. However, there is sufficient evidence to indicate that some curative benefit can be secured and that this therapeutic use should be reinvestigated. It may be that larger therapeutic doses should be given than have been used, and perhaps the limited supply, in the past, has prevented the administration of large enough amounts of convalescent serum.

SCARLET FEVER CONVALESCENT SERUM

The treatment of scarlet fever with convalescent serum was first practiced by Weisbecker in 1897. He used relatively small amounts of serum,

from 10 to 20 c c , but secured quite good results. A number of workers followed his example, but it was not until the advent of the Wassermann reaction gave security against accidental transmission of syphilis, that this study was pursued energetically. Larger amounts of serum were used (from 50 to 60 c c) with even more favorable results. The first trial in this country was by Zingher, in 1914, working with Park. Next followed work by Synnott (1917), another report by Zingher (1917) and one by Weaver (1918). Many reports since, in many countries, have shown the marked therapeutic value of pooled convalescent scarlet fever serum when this is given in large enough amounts and especially when administered intravenously early in the disease.¹ The beneficial results have been so definite that in article after article recommendations are made for the organization of agencies for collecting and distributing convalescent serum. Blood, yielding potent serum, can be drawn on the twentieth day after the onset of illness, provided the patient is convalescing and has been fever free for at least seven days, and further bleedings may be made at two or three week intervals for a period of four months and probably for as long as six months. About five years ago, with the cooperation of the Chicago Department of Health and of a number of colleagues, it was possible for me to organize the Samuel Deutsch Convalescent Serum Center at Michael Reese Hospital, and similarly a year ago the Milwaukee Convalescent Serum Center at Columbia Hospital. Some of the observations in Chicago have been published with Hoyne and Levinson.

Eight hundred and seventy-two children, giving no history of previous scarlet fever, and unavoidably exposed in their homes to this disease, were passively immunized with from 10 to 20 c c of pooled convalescent serum, and only 2.8 per cent developed scarlet fever. In similarly exposed home contacts, Park states that in his experience about 10 per cent contract scarlet fever, and Gordon's findings in Detroit were 15 per cent. Therefore, one can conclude that only one out of the expected four or six developed the disease. Stated in another way, convalescent serum protected from 75 to 83 per cent of those who without passive immunization would have contracted scarlet fever. Besides this, those who came down with this illness usually had it in a mild and modified form. In 83 Dick-positive hospital contacts, similarly immunized, only 5 per cent had scarlet fever. Because of the less direct nature of hospital exposure, this result is more difficult to evaluate.

The results of therapy have been published for 947 severely ill hospitalized patients and 983 home treated patients of varying degrees of severity, 1930 patients in all. The hospitalized patients were treated in the Chicago Municipal Contagious Disease Hospital under the direction of Dr. Hoyne. Only severely sick patients received serum, usually on admission, and 6,282 mildly or moderately ill patients, admitted to the hos-

* For complete review of the literature through 1930, see *Annals of the Pickett-Thomson Research Laboratory*, Vol. VI.

pital during the same period, treated symptomatically and not receiving serum, served as controls

Some of the findings can be briefly restated. Patients without septic complications showed an average fall of temperature of two and a half degrees in the first 24 hours and a total of three degrees in the first 48 hours when they received the convalescent serum within the first three days of their illness. Not infrequently there was a dramatic reduction of four to five degrees. When the serum was given from the fourth to sixth days of the disease the temperature drop was from one-half to one degree less. With the decline of temperature there was a corresponding and marked diminution of toxicity, fading or disappearance of the rash, relief from angina, nausea and vomiting, return of appetite, and shortening of the period of illness. Most patients with complications on admission or mildly ill but later developing complications were also benefited by serum but to a less degree.

The evidence definitely shows also that severely ill, serum treated individuals developed a smaller number of less severe complications than the mildly or moderately ill in the control group not receiving serum.

The dosage, depending on the size of the individual and the severity of the illness, varied from 40 to 100 c c. It was administered intravenously and occasionally had to be repeated. In the entire series no reactions occurred other than a few instances of mild urticaria. Intravenous administration is preferred to intramuscular injection because of rapidity of action and absence of reactions.

It may be of interest to note that excellent results have been observed by ourselves and others in the treatment with convalescent scarlet fever serum of various types of severe infection with hemolytic streptococci. Some of these results have been analyzed in a publication with Levinson. This would appear to be a profitable field of therapy and of further investigation. Immuno-transfusion, using adults recently recovered from scarlet fever as donors, has yielded some excellent results in very toxic patients with scarlet fever and also with various kinds of hemolytic streptococcus infections. This is a therapeutic agent which should have a wider use.

OTHER TYPES OF CONVALESCENT SERUM

More extensive investigation is much needed in the varied and important group of infectious diseases, especially as many small studies have yielded hopeful findings. Some of the convalescent serums referred to are for pertussis, pneumonia, typhoid fever, for vaccinia encephalitis, for complication of mumps, etc. Time will not permit presenting any tentative deductions from the literature or from personal experience.

SUMMARY

It seems clear that some convalescent serums, especially those for measles and for scarlet fever, having been demonstrated to have a consider-

able degree of usefulness, should be made generally available by the development of centers organized for their collection and distribution

These organizations also should be centers of investigation and research, under rigorously controlled plans, and should extend our knowledge not only of the value of convalescent serums for all infectious diseases but also of many fundamental immunological problems

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THE VALUE OF CERTAIN DIAGNOSTIC PROCEDURES IN BRONCHOPNEUMONIA: A CLINICAL STUDY^{*}

By JOHN V FOPEANO, A B , M D , *Ann Arbor, Michigan*

IN a day when clinicians depend much upon the clinical laboratory for guidance in diagnosis and prognosis, there is a need for data showing the limitations of the objective methods of the laboratory. Even the reliable clinical thermometer may sometimes lead one astray.

In a study of the cases of pneumonia which have occurred during the past two years among students at the University of Michigan, three things have stood out clearly:

- 1 Absence of leukocytosis in uncomplicated bronchopneumonia indicates neither a good nor a bad prognosis

- 2 It is possible and not uncommon to have bronchopneumonia without any detected fever

- 3 The clinical diagnosis of bronchopneumonia and even of lobar pneumonia can sometimes be made two days before roentgen-ray confirmation is possible

The records of 62 cases of pneumonia occurring during the past two years contained roentgen-ray studies, clinical records, and laboratory work, sufficient for use in this study.

All of the cases except one occurred in students at the University of Michigan, and in young adults who for the most part were without any important complicating physical defects. The one non-student was a staff member aged twenty-eight. All cases were hospitalized in the Infirmary of the Health Service. None of the cases received vaccine or serum treatment. The treatment was symptomatic, consisting of strict bed rest, special nursing care in the more severe cases, sedatives, high vitamin soft diets, and nearly always acetylsalicylic acid during the period of acute illness. There were no deaths. The cases occurred during the period of September 1933 to June 1935. The roentgen-ray films were read by the Department of Roentgenology of the University of Michigan Hospital. In each instance the case was followed with roentgen-ray until clearing was complete. No other diagnosis than pneumonia appeared reasonable.

NO SIGNIFICANT RELATIONSHIP BETWEEN LEUKOCYTE COUNT AND THE SEVERITY OF THE DISEASE

In describing bronchopneumonia textbooks on medicine nearly always point out the presence of leukocytosis. The absence of leukocytosis is interpreted as being either a bad prognostic sign, indicating the lack of resistance,

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or as the concomitant of a very mild infection. Even cases of influenza, normally having a leukopenia, are said to develop a leukocytosis when pneumonia appears as a complication if the resistance is good.

Early in our experience we were worried by the fact that cases of pneumonia so often failed to show a good leukocytic response. Later the frequency of low counts associated with a mild course of the disease led to a disregard of the white blood cell count and the number of polymorphonuclear neutrophilic leukocytes as indicators of the prognosis in pneumonia. These are still found useful as very early indicators of the development of complications.

In order to present this study of pneumonia in a graphic and mathematical manner, the severity of the disease has been expressed in terms of mortality, duration of fever, duration of hospitalization, and incidence of complications. All the cases were mild in the sense that there was no mortality.

The white blood cell count on the day of the highest fever has been used, since that is the time when the patient is usually considered sickest and it is then that the doctor is looking for a sign which will help to indicate the prognosis.

Chart 1 shows the height of the total white blood cell count on the day when the fever was at its highest point, plotted to show the duration of the fever in days. Chart 2 shows the total white blood cell count on the day of highest fever and the length of hospitalization.

A little study of the scatter maps, or statistical handling of the data they represent, reveals that about half of our cases have counts under 10,000 at the height of their fever, and that on the average the cases with higher leukocyte counts have no shorter or longer duration of fever or of hospitalization than those cases having no leukocytosis. There does, however, seem to be an increase in the incidence of complications in those who have low counts at the height of their fever. Seven complications occurred among 32 cases having counts of 10,000 or below, whereas complications occurred only twice in the 30 cases having counts of more than 10,000 at the height of their fever. The number of cases having complications is too small to permit any conclusions, because such a distribution of the white blood cell counts in a small series could quite often occur by chance. All of the cases developing complications showed a moderate to marked leukocytosis coincident with the development of the complication.

Handling these data in a way to show the standard error of the difference between the two variants reveals no significant correlation.

Another study (charts 3 and 4) was made, using the number of polymorphonuclear leukocytes instead of the total white blood count. This likewise showed no significant relationship between the height of the count on the day of highest fever and the duration of the fever or the length of hospitalization.

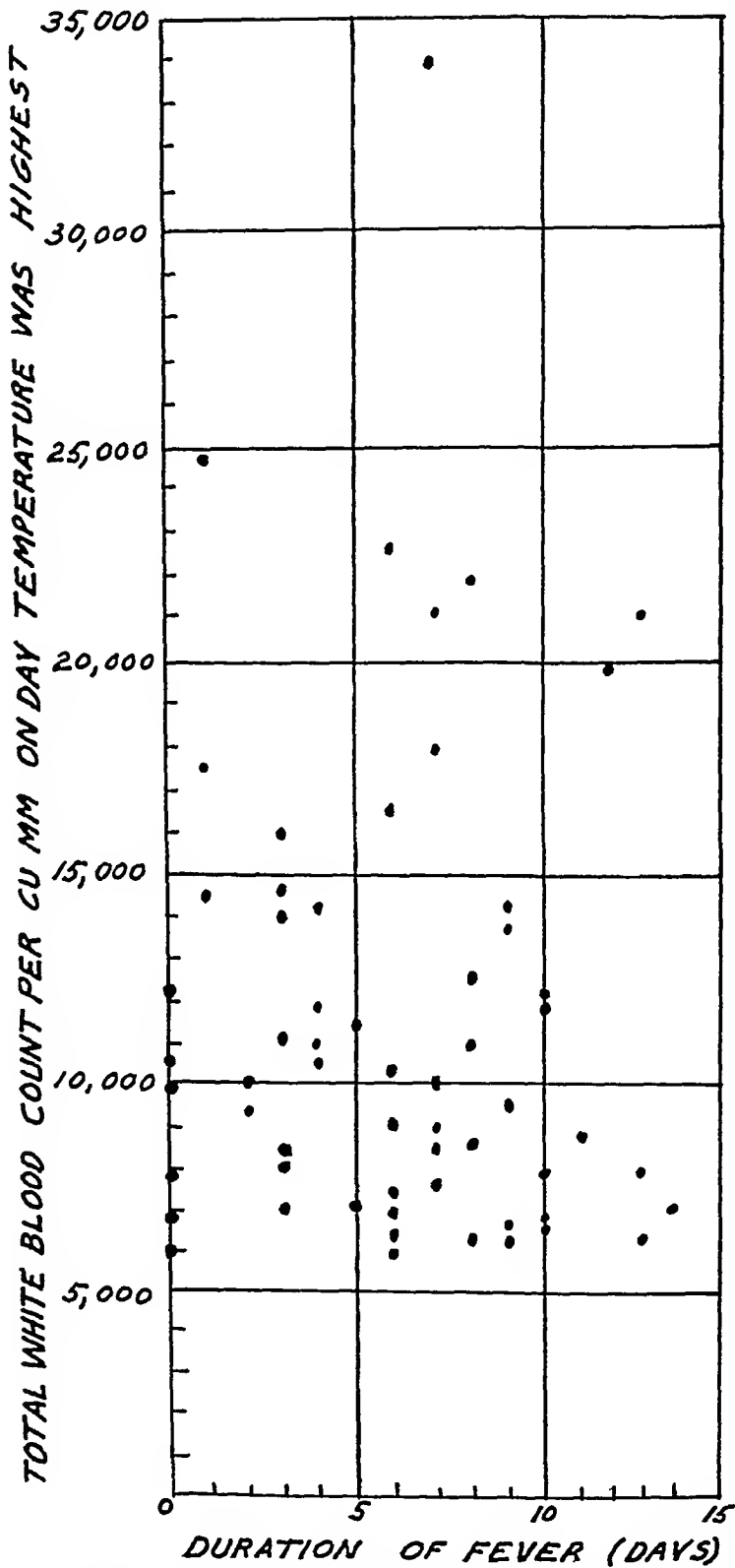


CHART 1 Pneumonia in University Students. Relationship between the total leukocyte count on the day of the highest fever and the duration of the fever in days. Dots represent cases

THE HEIGHT OF THE WHITE BLOOD COUNT AND THE ETIOLOGIC AGENT OF PNEUMONIA

In only 25 of the cases was successful isolation of an organism from the sputum accomplished. The organisms found were Pneumococci Types I, II, and IV, Pneumococcus type undetermined, *Micrococcus catarrhalis*,

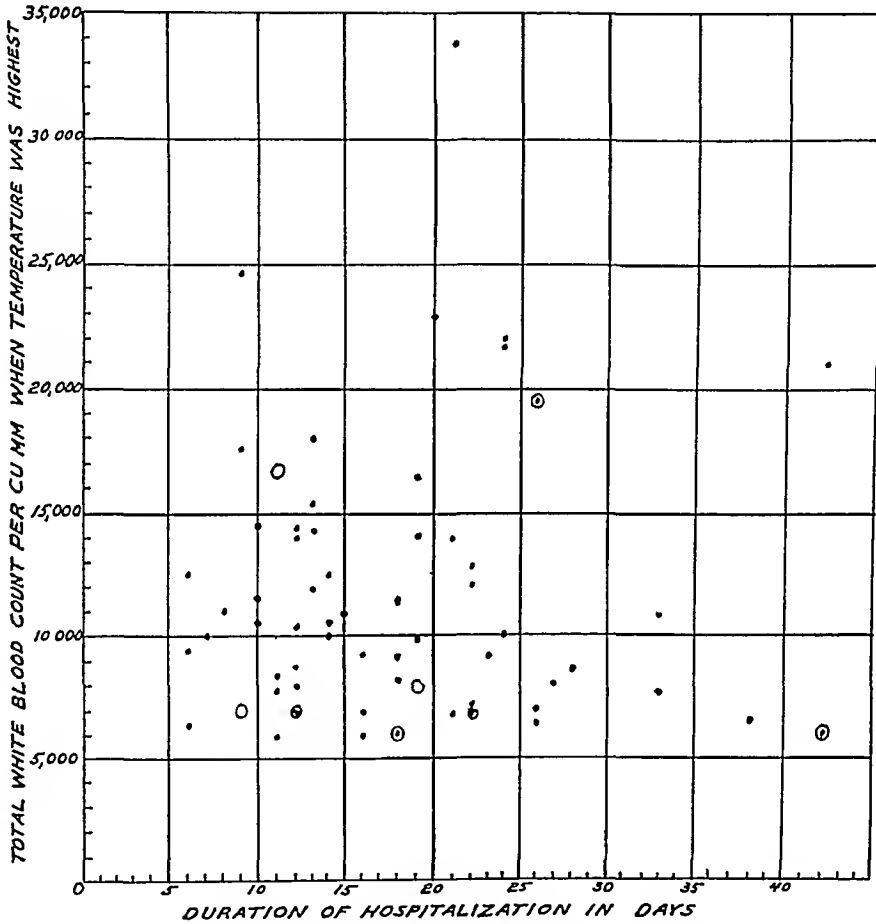


CHART 2 Pneumonia in University Students Relationship between total leukocyte count at the time of the highest fever and the duration of hospitalization in days. Dots represent cases and those surrounded by a circle indicate cases in which complications developed. All of these cases having complications developed moderate leukocytosis with the onset of complications.

Streptococcus viridans, non-hemolytic streptococcus, *Staphylococcus aureus*, and gram-positive cocci unidentified. There was no significant relationship between the type of organism and the blood counts. However, the number of cases is much too small to permit any definite conclusions regarding a correlation between white blood count and type of organism recovered in the sputum.

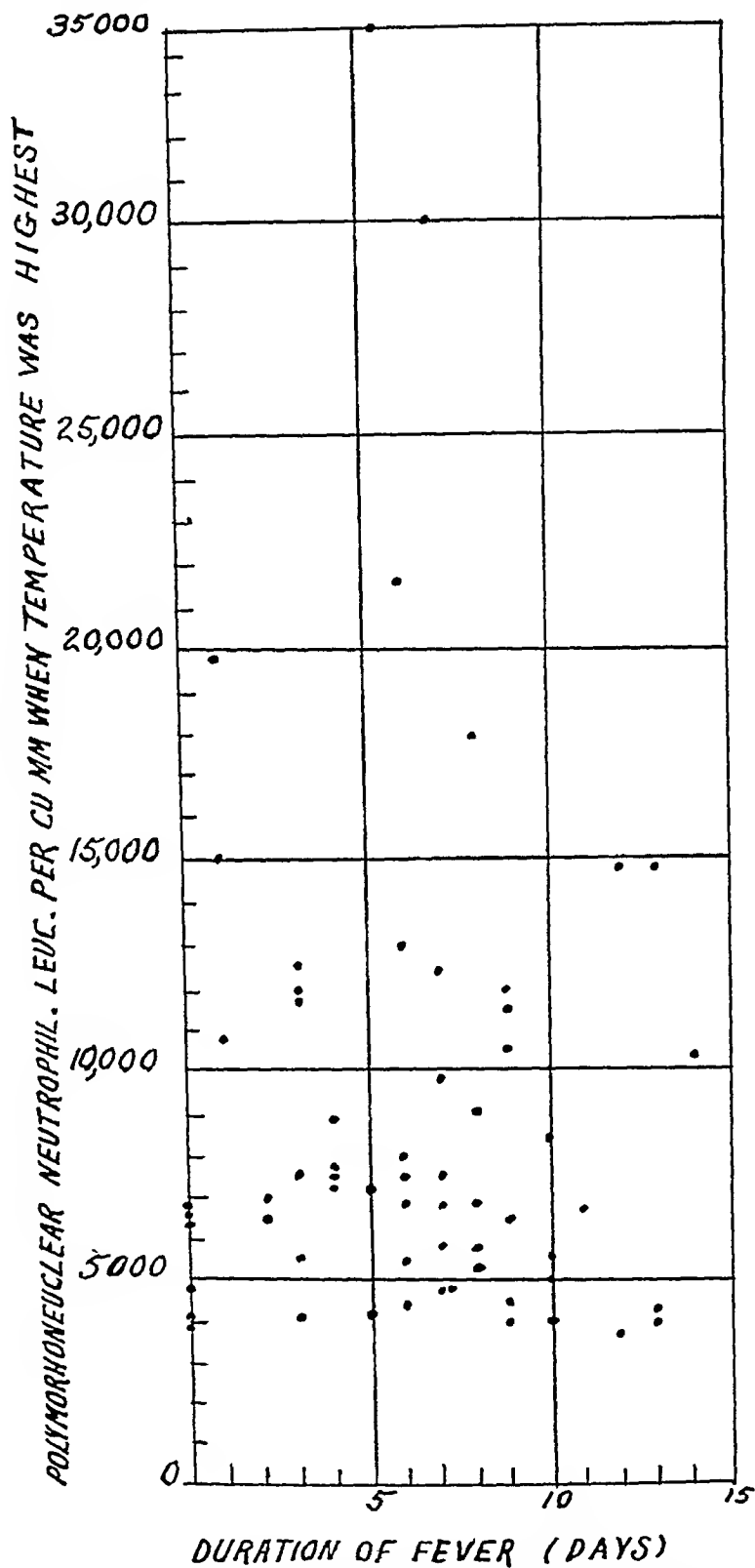


CHART 3 Pneumonia in University Students Relationship between the polymorphonuclear neutrophilic leukocyte count on the day of highest fever and the duration of fever in days Dots represent cases

THE HEIGHT OF THE WHITE BLOOD COUNT AND THE KIND OF PNEUMONIA

Only five of the 62 cases were diagnosed as lobar pneumonia. In these five cases the polymorphonuclear count at the height of the fever varied from 4,000 to 14,000, and here again there was no relationship between the height of the white blood cell count and the duration of the fever or hospitalization.

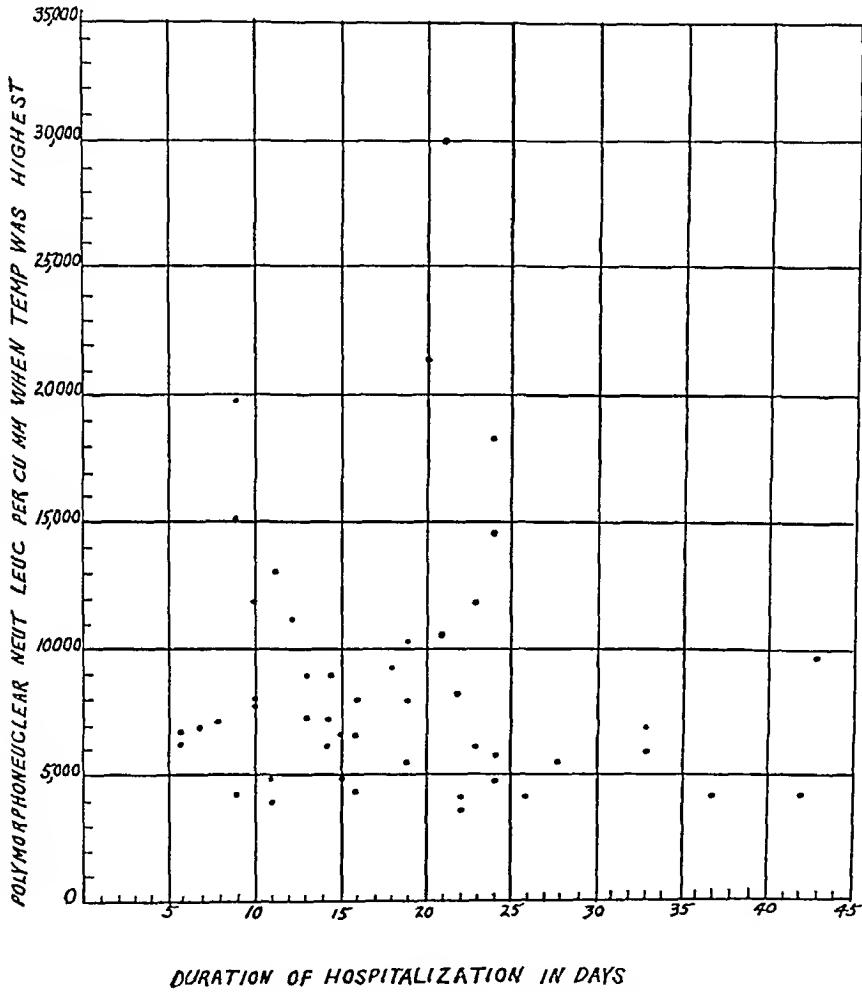


CHART 4 Pneumonia in University Students. Relationship between the polymorphonuclear neutrophilic leukocyte count at the time of highest fever and the duration of hospitalization in days. Dots represent cases.

PNEUMONIA WITHOUT FEVER

Six patients had no fever during the period of hospitalization. These afebrile patients were examined by roentgen-ray because they had physical signs (râles) or symptoms such as cough, general malaise, or pain in the chest. The diagnosis was made by means of roentgen-ray and the sub-

sequent behavior of the shadow allowed no other interpretation of the films. The shortest period of hospitalization was six days and the longest fourteen. The period of hospitalization was determined by the length of time necessary for complete disappearance of roentgenographic shadow. None of these cases had any complications. Three of the cases had white blood cell counts which remained below 8,000 and three had blood counts between 10,000 and 12,000. The causative agent in four cases was not determined due to lack of sputum and the mildness of clinical symptoms. In one case a pneumococcus (type unknown) was obtained and in another a mixture of *Micrococcus catenulatus*, *Staphylococcus albus*, and non-hemolytic streptococcus. All were reported as bronchopneumonia involving a single lobe.

CLINICAL PNEUMONIA WITH DELAYED APPEARANCE OF ROENTGEN-RAY FINDINGS

In this series there have appeared eight cases in which a clinical diagnosis of pneumonia was made but which had negative roentgenograms until after the third day. Two of these cases had lobar pneumonia and six broncho- or lobular pneumonia. All of them were confirmed when roentgen-ray films were made on the third to the ninth days. *In the same breath it must be emphasized* that in many instances pneumonia was not diagnosed until the Department of Roentgenology made its report.

CONCLUSIONS

Conclusions derived from this study of 62 cases of pneumonia in University students are as follows:

- 1 White blood cell counts between 6,000 and 35,000 and total polymorphonuclear neutrophile counts between 4,000 and 30,000 when the temperature is highest, are not indices of the prognosis as to duration of fever or hospitalization, or as to complications.

- 2 The height of the leukocyte response does not appear to be determined by the kind of organism recovered from the sputum or by the lobe involved. The number of cases of multilobar involvement and lobar pneumonia encountered is too small to permit conclusions, but it is not uncommon to have low counts even in lobar pneumonia.

- 3 It is possible and fairly common to have bronchopneumonia without any detected fever.

- 4 The clinical diagnosis of bronchopneumonia and even of lobar pneumonia can be made sometimes two days before roentgen-ray confirmation is possible.

- 5 It is a very common experience to have roentgen-ray evidence of bronchopneumonia without clinical signs of the disease.

WHAT THE PHYSICIAN SHOULD KNOW ABOUT DENTAL PROBLEMS¹

By WM J KERR, M D , F A C P , *San Francisco, California*

IT is indeed an auspicious occasion which brings together the dentist and the physician. They have too long traveled independent courses to the detriment of each. The schism which led to the development of modern dentistry is so recent that most of us can recall the family doctor who practiced dentistry as a "side line". His efforts were directed chiefly toward the relief of pain in an aching tooth. When he failed in this, the ever ready forceps in his medical kit came into action. The village blacksmith was also handy with his tongs or with the punch and a well directed blow of the hammer. I must confess to personal transgressions upon the province of the dentist when, a few years ago as a ship's doctor, I was obliged to remove two remarkably loose teeth from the mouth of a wayfare. This was done to prevent him from aspirating them during sleep. My activity in the dental field, however, has been confined chiefly to the timely plucking of deciduous teeth from our four children with due foresight to cooperate with the fairies and place a quarter of a dollar under the pillow at night as a reward for the sacrificed tooth. We have done our share to support the manufacturers of tooth-brushes and dentifrices and to inculcate from birth good habits for the proper care of the teeth. We have also tried to provide the elements of diet which aided in the development of the teeth and jaws and their preservation. These efforts have not met with favor by the youngsters but have been taken on faith. The periodic visits to the dentist have revealed our shortcomings and after frequent repairs the outgoings from the purse have been considerable. However, we have preserved full dentures with satisfactory function. For ourselves and our parents we have striven to preserve what was left of our permanent teeth after a poor start in childhood, and have replaced the missing members which have been sacrificed upon the altars of negligence and time. We have, no doubt, leaned heavily on our dentist for restoration of function but, certainly, we must confess to some solicitude for looks and the enjoyment of a savory bolus, well chewed. We must also confess to frequent surprises when our dentist reminded us that it was past time for a visit to his office to look over the "tombstones". This sounded like business for the dentist and one wondered at his trustful nature when we had just finished paying for the last visits.

Having detailed a few personal experiences and confessions, it may be proper to ask what the average physician knows about dental problems. In the first place he knows about what the average citizen knows, or a little

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more If he hasn't been out of medical school too long, he knows something about the development of the teeth from his course in embryology His knowledge of the anatomy or structure of the teeth is sketchy and his acquaintance with the diseases of the teeth is gained through a reversed perspective in the examination of the mouth in his patients He is obliged to learn the dates for the eruption of the deciduous teeth for anxious young mothers, subject always to correction by experienced grandmothers He has a passing knowledge of gross changes shown by roentgen-ray films—often poorly taken

The average physician pays scant attention to the teeth and other parts of the organ of mastication unless they are seriously and obviously diseased He knows that in certain instances the teeth and adjacent structures may act as foci of infection, in fact, he has been too enthusiastic on this point during the last generation The result has been the wholesale sacrifice of doubtfully offending and often of sound teeth The physician has been too ready to advise extraction of teeth without a thought to the limits of the dentist in restoration This practice, urged by well meaning physicians who saw only one side of the shield, has happily been limited in recent years under the influence of dentists of better training who look upon the tooth as a living organ Physicians, also, have learned more about the value of methods of body-building which favor the control of local processes At a higher level of general well-being the small foci of disturbance are controlled and are no longer a menace to health

Current medical literature is filled with discussions on metabolic disturbances, disorders of the endocrines, and the action of the vitamins, which may affect the integrity of the teeth and contiguous structures The physician and likewise the dentist are intrigued by the prospects Unfortunately, fancy too often overruns the facts The sins which are committed in these fields of therapeutics are numerous and, until we have more accurate scientific information, the chief beneficiaries are the pharmaceutical houses, which put up their products in such delectable forms and at fancy prices

The public is conscious of the great achievements in science They eagerly and innocently accept the pseudoscientific statements blazoned forth in advertisements of nostrums and "curealls" Both medical and dental practitioners have lent their names, unfortunately, sometimes inadvertently but usually for gain, to this class of propaganda They would have us believe that oral antiseptics really have some value and that some particular dentifrice is superior to all others when it is the peculiar odor, flavor or color which we enjoy They play upon our fastidious natures since we wish to be socially acceptable It is high time that we take the leadership in this matter The public should look to the dentist and physician to keep abreast of scientific knowledge and to give advice in all matters pertaining to health

An increasing number of physicians are interested in dental problems. The general practitioners and specialists of sorts in every branch of medicine. They and those who limit their practice to certain fields, the specialists, are busily checking their clinical experience against the discoveries in the experimental laboratory. The more forward dentists are, likewise, interested in the problems and in many directions have actually assumed leadership. Their interest arises naturally from a desire to seek the causes for the diseases and conditions which they are called upon to treat. They do not wish to become general practitioners of medicine but they rightfully insist upon recognition as specialists in medicine. The technical procedures employed in dentistry require special knowledge and training but the future field of the dentist does not end there.

We may now ask what the physician should know about dental problems. Naturally, he is not concerned with technical procedures unless they directly affect the general health of the patient. Certain dangers may be encountered if in the execution of dental care poisonous substances are used, unsafe or ill advised anesthetics may be employed in a given case, or infection may be introduced.

The physician should know that the teeth and supporting and sustaining structures are living parts of the body and deserve due respect. They are capable of growth and repair, and die when not properly nourished. They may be injured or destroyed by accident, disuse, disease or faulty care.

The teeth are most important parts of the organ of mastication. They operate in a systematic manner to prepare the food on its route to the digestive tract where more intricate functions are performed. When one comprehends the manner in which the jaws, muscles, cheeks, lips, tongue, salivary glands, and the teeth cooperate to handle the bolus of food, he can understand the enthusiasm which led to Fletcherism of by-gone days. One can live on foods which do not require mastication, but so can people live without stomachs and with a large part of the bowel removed, but none would agree that these individuals are properly nourished.

The modern tendency to use prepared and predigested foods is, no doubt, giving rise to faulty development of the face, jaws and teeth through lack of use. The "rugged individualism" in which most Americans take pride will not apply to their powers of mastication. The pap which is served from the cradle to the grave will make of us a race of facial weaklings.

There can be no doubt that heredity influences the organs of mastication. The shapes of jaws, the configuration of the teeth, their number and positions are modified through such factors. The quality of teeth likewise appears to be inherited, but it is possible that habits of eating and quality and quantity of food in a family group are the factors which operate and are mistaken for the influence of heredity in such cases. At present we can do nothing to control hereditary factors except in those diseases like hemophilia where known bleeders can be prevented from begetting offspring. There is a rare inheritable disease known as dysostosis-cleido-cranialis, which is due

to a disturbance in the formation of bone in the sixth week of intrauterine life and just before the teeth begin to form. In such cases the skull is improperly formed, the development of the teeth and jaws is retarded and never becomes normal, the clavicle is frequently present in only the central portion and other membranous bones are imperfectly formed. At present there is no known way to prevent this disease, which may occur in several generations, except by contraceptive measures.

There are a number of congenital diseases which are known to influence the teeth and buccal tissues. Chief among these is syphilis which distorts the palate, gives rise to imperfect formation of teeth and to scarring of the lips. This misfortune is preventable and the means are in the hands of the physician who cares for the parents. Among the metabolic diseases are rickets and cretinism where preventive measures during pregnancy may correct the defects in the growing fetus, in the first instance by the administration of adequate calcium, phosphorus and vitamin D, and in the other by the use of iodine or thyroid extract by the expectant mother.

At the time of birth the well trained obstetrician should know that injuries to the jaw and facial nerve may result from faulty application of forceps, which may lead to abnormal mastication later in life.

The physician should know that the teeth are formed early in the life-history of the individual and that prenatal and early post-natal influences are most important for proper growth. It appears to be well accepted that breast fed babies have better teeth than those fed on a bottle. Infants should have something to masticate as soon as they have the tools to do so and probably require something firmer than milk to aid in the proper development of the jaws and the eruption of teeth. If a greater variety of food-stuffs were offered to infants during the young robin age, perhaps when they are older, children wouldn't be so particular about things we think are good for them—even spinach. Most liquid diets or pappy diets served to infants and young children are relatively inadequate in certain particulars. Human milk from healthy mothers is the most perfect food for the new-born child.

Physicians and mothers should know that if an infant sleeps constantly on the face or on its hand, the bony structures of the face may be deformed, resulting in defective support for the teeth. Thumb sucking may likewise deform the palate and other structures.

As the child becomes older, there are increasing demands for substances which promote growth until the great epoch of puberty, when such processes are at their height. In the osseous structures, including the teeth, there is need for minerals and chief among these are calcium and phosphorus. There must be adequate supplies of other extrinsic factors such as growth-promoting vitamins. The internal organs which provide for the digestion, absorption, elaboration and storage of these substances must be functioning properly. The ductless glands, especially the pituitary, thyroid and parathyroids, and perhaps the gonads, must be relatively normal if growth, with

its checks and balances, is to be favorable. The ravages of constitutional disease and the exanthemata may distort the normal progression of events and frequently do so, leaving mementos in the more permanent structures such as the bones and teeth.

It is at this stage of greatest growth when dental caries is encountered. The modern trend is to attribute such disorders to nutritional disturbances in a broad sense and perhaps to a decreasing extent to local and environmental conditions in the mouth. It may well be that both factors are operative. Far be it from me to take sides in a highly controversial field. The relative immunity of certain groups to dental caries would suggest that nutritional factors are important. The universal loss of most of the teeth early in life in certain sections of the British Isles led a young American soldier to a pointed remark during the World War. In speaking to a fellow soldier after a day of leave he remarked, "I have just kissed the prettiest girl in Scotland and she had a full set of teeth—one above and one below." It would appear reasonable to assure ourselves that growing children are supplied with all the known factors for adequate growth and development and at the same time to care for the teeth and their environment to the best of our ability.

We are just now emerging, we hope, from a period of great nutritional deprivation for many millions of our population. We have seen a few examples of nutritional diseases in an exaggerated form among them but how many are experiencing subclinical types of deficiency disease there is no sure way of knowing. It is likely that dental defects for many decades to come can be attributed to these years of undernutrition. It will be difficult to trace, however, in view of the long time required for the younger sufferers to reach maturity. Fortunately, those charged with the administration of relief have given some thought to balanced rations but where cash-relief has been given, most of the money has been used for the purchase of the cheapest food-stuffs, which are carbohydrates. The deductions for alcohol, tobacco, confections and cosmetics also limit the total funds available for purchase of essential food-stuffs.

A group that may benefit from the depression are those individuals who tend toward adiposity. Here the general health may be improved by restricting the diet, provided their ration is properly balanced.

There are certain constitutional disorders which give rise to local disturbances in the mouth and teeth. We are well aware of the spongy gums of the patient with scurvy (due to lack of vitamin C) and the historical accounts of sufferers from this disease in the olden days of discovery are familiar to all. Happily we see few outspoken cases today where teeth loosen and fall out, but mild scurvy may exist among our undernourished population. The dentist may be the first to encounter this condition.

The relationship between rickets and deficiency of vitamin D is well known. We recognize the importance of adequate intake of calcium and phosphorus, ultraviolet light, and normally functioning parathyroid glands.

in the growth and deposition of bone. Recently we have learned that bile salts must be excreted with the bile to permit vitamin D to pass into the system. The pregnant woman has unusual demands for materials to build the skeleton and teeth of the fetus, and in experimental studies the pregnant animal actually shows a negative balance for calcium unless it is supplied in abundance and other factors are harmonious. The penalty for pregnancy is destruction of teeth in the mother. If supplies for the growing fetus are inadequate, the infant suffers, also, throughout the osseous structure and this lack often appears in defective development of jaws and teeth. Rickets and scurvy are but two of the deficiency diseases which give rise to dental problems. Deficiencies in vitamin A, which appear to be important in preserving epithelial structures, may give rise to dental defects but our present information is inadequate on this point.

Diseases of the ductless glands no doubt are important in causing defects in the jaws and teeth but our present knowledge about them is rather chaotic. Over-production of the growth-hormone after puberty certainly distorts the jaws and leads to malocclusions and separation of the teeth with other disturbances in growth of the local tissues. Hypofunction of the pituitary (Simmond's disease) may result in underdevelopment of the organs of mastication or a regression of local tissues in general. Hypo-thyroidism is a potent factor for underdevelopment in utero and in childhood but less significant in adult life when secondary changes may be caused by underfunction of the thyroid. The parathyroid glands may, rarely, become hyperplastic or may be the site of adenomas which cause hyperfunction. This disturbance leads to cyst formation and general fibrosis in the bones, and in this process the jaws may share. We have seen a number of such cases in the past few years.

All constitutional diseases which lower the general vitality may affect the jaws, gums and teeth and interfere with their proper nourishment. Local lesions may also occur. Tuberculosis and syphilis are examples of this type, the latter especially exhibiting destructive processes in the palatal and facial bones.

The heavy metals, entering the body by accident or intent as therapeutic agents, are frequent causes of destructive lesions in the supporting structures for the teeth. Mercury is notorious for its action in causing salivation and the loosening of teeth. Lead, bismuth and copper likewise cause local changes and are deposited in the margins of the gums in untidy mouths. Radium and other radioactive substances are dangerous to the bones of the jaws and other local tissues, as we have learned from the experiences of workers in factories where dials are marked with illuminated paints. In such work the brushes are kept pointed by frequent contact with the lips. Arsenic, when applied locally, may cause necrosis of local structures and lead to chronic ulcerations. Iron is frequently used in the treatment of anemia and it is well known that local discolorations of the teeth may result. This is apparently not due to contact with the teeth in taking the drug but enters by way of the circulation.

The elements phosphorus and fluorine have interesting effects on bones. Fortunately, phosphorus has ceased to be a frequent cause of necrosis of the jaw since its use in certain compounds has been prohibited in the manufacture of matches. Fluorine, the salts of which are among the most soluble substances known, is a normal ingredient of teeth. When ingested in excess, however, marked overgrowth of periosteum and deposition of collars of bone occur outside of the normal bone. Such overgrowths may be seen in the jaws and peculiar mottling of enamel may be noted. These defects occur in districts where the content of fluorine in the drinking water is high. Water containing more than 1 milligram per cent is considered unsafe for drinking purposes. The malady affects the enamel during the preeruptive period. At present there is no known way to remove excessive amounts of fluorine from the water and some other source of potable water must be found. We should be extremely cautious in choosing a water-supply from certain regions of the Rocky Mountains.

Mention has already been made of hereditary bleeders, or hemophiliacs. It is common knowledge that the royal families of Spain and Russia were afflicted with this disease. The physician should know the dangers of fatal hemorrhage resulting from the extraction of teeth in such cases and should cooperate with the dentist if necessary technical work is to be done.

A disease of the blood and blood-forming organs, known as leukemia, frequently manifests itself first in the gums with hemorrhage. The dentist may be called upon to treat the local condition. The physician attending such patients should warn the dentist in advance of the dangers of radical treatment of the gums and teeth until this fatal disease is under temporary control.

Cancer and sarcoma may arise in the lips, gums, teeth, jaws or other structures in the mouth and interfere with the function of mastication. The physician, in such cases, usually looks upon the dental problem as a secondary one in view of the rapidly fatal course of the disease. However, in some protracted cases and especially if destructive operations are necessary, the active cooperation of the dentist is imperative.

In fractures of the jaw the problems of early approximation of fragments, the realignment of teeth, and prevention of infection are of major importance. Here is the opportunity for real intelligent teamwork between the physician and dentist. Often in complicated cases extractions are necessary and reconstructions are useful.

We now come to a brief discussion of focal infection. There can be no doubt that focal infection in the mouth and elsewhere may give rise to serious constitutional disease. From the writings of Hippocrates, Dryden,* Benjamin Rush and Billings and his followers, we have become

* Dryden, "The throttling quinsy 'tis my star appoints,

And rheumatisms descend to wrack my joints"—Suggestion from Dryden before the year 1700, showing connection between focal infection (quinsy) and rheumatism. Mentioned by Dr. M. H. Dawson.

aware of their frequent association. That the practice of wholesale removal of teeth for suspected foci has been overdone needs no emphasis before this group. I have already mentioned the observations indicating that local lack of vitality may result from constitutional disease. There can be no argument with those who wish to remove a proved focus of infection for its own sake but in practice we have too often mistaken the cart for the horse. In any group of debilitated people we will find many who show several foci of infection and these local lesions are not limited to the teeth and surrounding structures. If we can build up these patients generally, the local processes will usually become insignificant.

The problem of pyorrhea alveolaris or, to use the more non-committal term, paradentosis, is still unsolved. How much of a rôle infection plays as a primary factor is undetermined. There is no doubt that infection may localize in the tooth and around the tooth, may extend to the soft tissues, and may penetrate the bones themselves. The physician who may see the patient first should be aware of the dangers of untreated infection and secure the advice and cooperation of the dentist at the earliest possible moment. It has been my experience, on a number of occasions, to hear of some patient with osteomyelitis of the jaw who sustained a fracture during the extraction of a tooth. The explanation is that the patient usually goes to the dentist for "tooth-ache" and if proper roentgen-ray films are not made, the involvement of the mandible is not revealed. It is the duty of the physician to know that in such cases the mandible is riddled with osteomyelitis from the time first seen, and that such results come from neglect of infected teeth or alveolar processes. The dentist is rarely to blame for such fractures. The destruction and deformity resulting from osteomyelitis of the jaw are frequently extreme and a satisfactory outcome is a credit to medico-dental cooperation.

Actinomycosis of the jaw is an infectious disease rarely seen in man. The problem is a difficult one and the results may be unsatisfactory.

Vincent's infection interests both physician and dentist. Too often the physician fails to recognize or treat properly the local infection in the mouth. The well trained dentist should be asked to cooperate. General measures may also be necessary and require the assistance of the physician.

Chronic atrophic or deforming arthritis and dental infection are frequently linked in our treatises. After many years of enthusiasm and frequent disappointment, the best medical viewpoint has shifted toward conservatism. If bacteria are agents in the cause of the arthritis, no one organism has been shown to be specific. We are now seeking more general or endogenous causes for this disease. Recently a deficiency of vitamin C has been suggested and this may well be a factor in causing the changes in the joints and in the periodontal tissues resembling mild scurvy. Further study will be needed to solve these problems.

In the foregoing remarks I have tried to show a few of the diseases encountered by the physician which introduce dental problems. With these, at

least, the physician should be familiar. From the numerous studies being undertaken in clinics and laboratories will come light upon the solution of the many problems which vex us. It is to be regretted that workers in the medical sciences have neglected a most important part of the body. Fortunately, those few whose training has been along dental lines are making notable contributions in this field. When physicians recognize the importance of the organ of mastication for the welfare of the body as a whole, there will be further contributions from the medical profession.

This brings me to my closing remarks which pertain to the future of dentistry. It is inevitable that the training of dentists will begin on a wider basis of scientific education. The preclinical sciences, as organized in the medical schools, will be prescribed with such training in the clinical branches as may be required to acquaint the student with man as a biological unit. His deviations from the normal which constitute disease will demonstrate the man out of health. The great field of preventive medicine will be unfolded for the dental student. The technical procedures which are required will be developed along the way but his mastery of them will come after his biological concepts are well grounded. Dentistry will then become more than a craft. The dentist will be, in fact, a specialist in medicine and on an equal footing with other medical specialists. The changes now going on in the dental schools of this country are healthy signs of a new order. All forward looking physicians should be ready to give encouragement and active support. What the country needs is not more physicians and dentists but better ones. We must cooperate to set high standards of professional attainment. We must harness science to our uses in the practice of our art. The resources of knowledge are almost unlimited. Anyone who is observant today knows that the discoveries of the future will dwarf those of the past. May the dental profession share in these epoch-making contributions.

CASE REPORTS

A CASE OF DIAPHRAGMATIC HERNIA IN WHICH MARKED CYANOSIS AND DYSPNEA WERE THE PRE-DOMINATING SYMPTOMS

By HENRY F STOLL, M D , F A C P , *Hartford, Connecticut*

IT is of more value to the clinician to be acquainted with the varied clinical pictures which may be caused by a diaphragmatic hernia than to be fully informed as to the details of its anatomical features, or as to the various proposed classifications of diaphragmatic defects. In the instance to be reported, the presenting symptoms and signs were unusually misleading, and it is from this point of view that the case seems worthy of record.

E V, female, aged 50 years, was admitted to the Hartford Hospital on May 9, 1935, and died on May 10, 1935.

Chief Complaint Shortness of breath

Present Illness Prior to one month ago the patient apparently had been in excellent health. At that time she began to have some dyspnea on exertion. She minimized her symptoms, and the family was not alarmed until about a week before admission when the skin began to have a dusky color. She refused to have a doctor called until just before admission, as she claimed she "felt well." However, a slight edema of the ankles was noted for the last two weeks of her illness and she also had a slight cough. There had been no nausea, vomiting or any complaint of pain though she had taken only liquid for a few days prior to admission.

Physical Examination Fairly well-developed and nourished woman with extreme cyanosis suggesting somewhat chronic acetanilid poisoning. There was no adenopathy or thyroid enlargement present. Respiratory excursion of the left chest was almost entirely absent. Over the lower two-thirds of the left chest anteriorly and posteriorly there was a flatness with absent voice and breath sounds. One observer detected a small area of tympany over the left apex on percussion. Over the right chest the breath sounds were very much exaggerated and there were moist râles throughout the lower half. Heart was displaced markedly to the right. Rhythm regular. Sounds were of "tick-tack" quality. No murmurs heard. Blood pressure on admission was 190 systolic and 88 diastolic, subsequently it was found to be 135 systolic and 80 diastolic. Spleen not felt. No demonstrable fluid wave in the abdomen. There was considerable edema of the lower extremities.

Urine specific gravity 1.014, albumin plus 3, numerous hyalin and granular casts.

Subsequent Course Four unsuccessful attempts at thoracentesis in various areas were made, only 5 cc of thin, blood-tinged fluid being obtained. The patient was immediately put in an oxygen tent with considerable temporary improvement in the cyanosis. Pulse was of good quality, 92 to 104. Respirations were rapid and shallow. Notwithstanding stimulation, the patient died about 30 hours after admission.

* Received for publication November 13, 1935

The cyanosis and dyspnea were so extreme that before making an examination, one wondered if one were dealing with a case of Ayeiza's disease. However, the physical signs seemed conclusive of massive hydrothorax. The patient's age and the relatively insidious onset seemed to favor an effusion associated with a malignant growth, though an effusion of tuberculous nature and a hydrothorax from cardiac failure were also considered. Our impression, however, was that the cardiac failure was not primary. The roentgen-ray

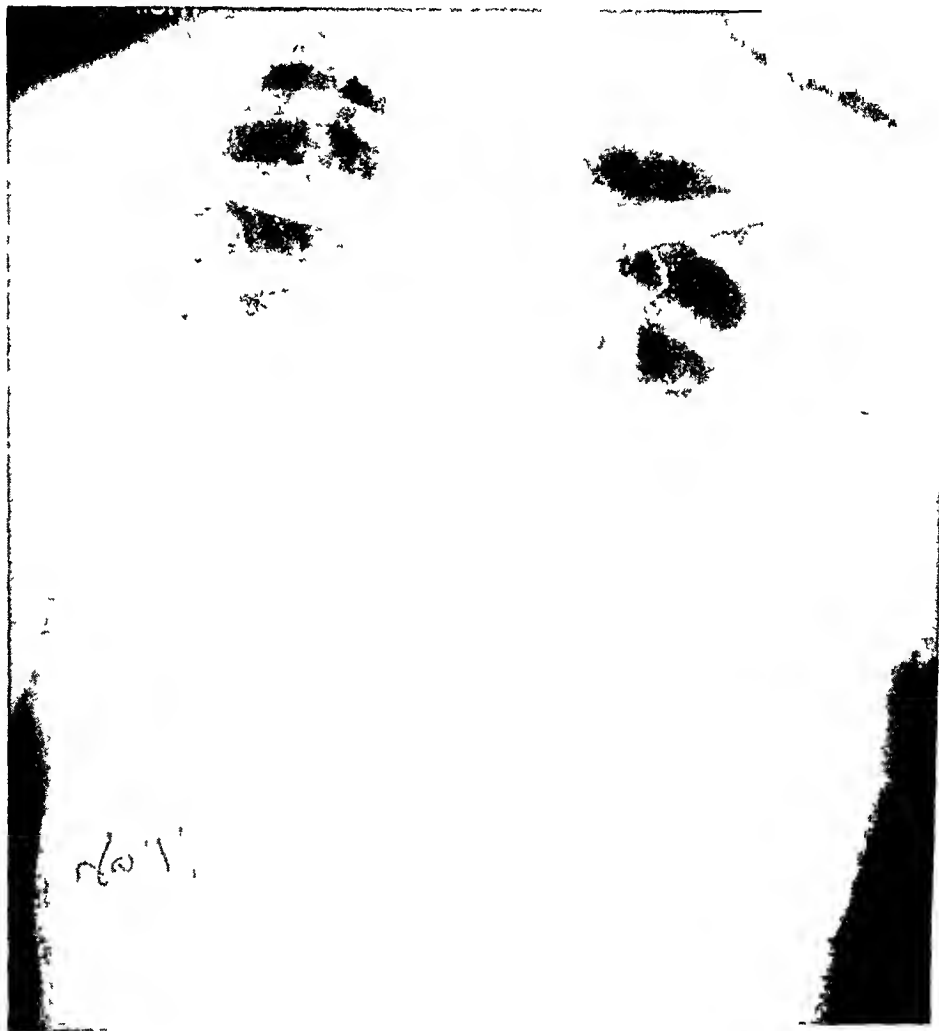


FIG 1

films were a good deal of a surprise in that they did not show as much fluid as the degree and extent of dullness suggested but they revealed a large amount of air which could not be demonstrated by physical examination. The conclusions of the Roentgenological Department were "A left-sided hydropneumothorax with evidence of old fibrotic infiltrative changes in and adjacent to the right hilum together with arteriosclerotic changes in the aortic arch."

The note of Dr. Morris T. Root, who examined the patient with me shortly

after admission, expresses our confusion "Even after seeing the roentgen-ray, I was unable to elicit resonance over the upper part of the chest where air was reported, also I could not elicit succussion sounds. These facts, with the absence of fluid in chest tap, I was totally unable to account for"

Notwithstanding the fact that the previous health of the patient was stated to have been good, it was felt by most of those who saw her that there was probably a malignancy present with mediastinal involvement and some unusual



FIG 2

FIGS 1 and 2 Both the postero-anterior and lateral views show air and fluid within the left pleural cavity and marked displacement of the heart to the right. The air is within the stomach and the fluid is the gastric and intestinal contents. The spleen and pancreas contribute to make the dense shadow below. There is also a suggestion of old infiltration at the hilus of the right lung. The right lower lobe appears partially atelectatic.

thickening of the pleura which prevented the fluid from being obtained and the usual signs of hydropneumothorax from being elicited Yet no one felt at all sure as to what was the underlying cause

Immediately following death, the house physician, who was much disturbed by his failure to obtain fluid, made further attempts Thinking he had previously not gone low enough, he introduced the needle first into the ninth interspace, two inches from the spine, and obtained about 400 c.c. of cloudy, cafe-

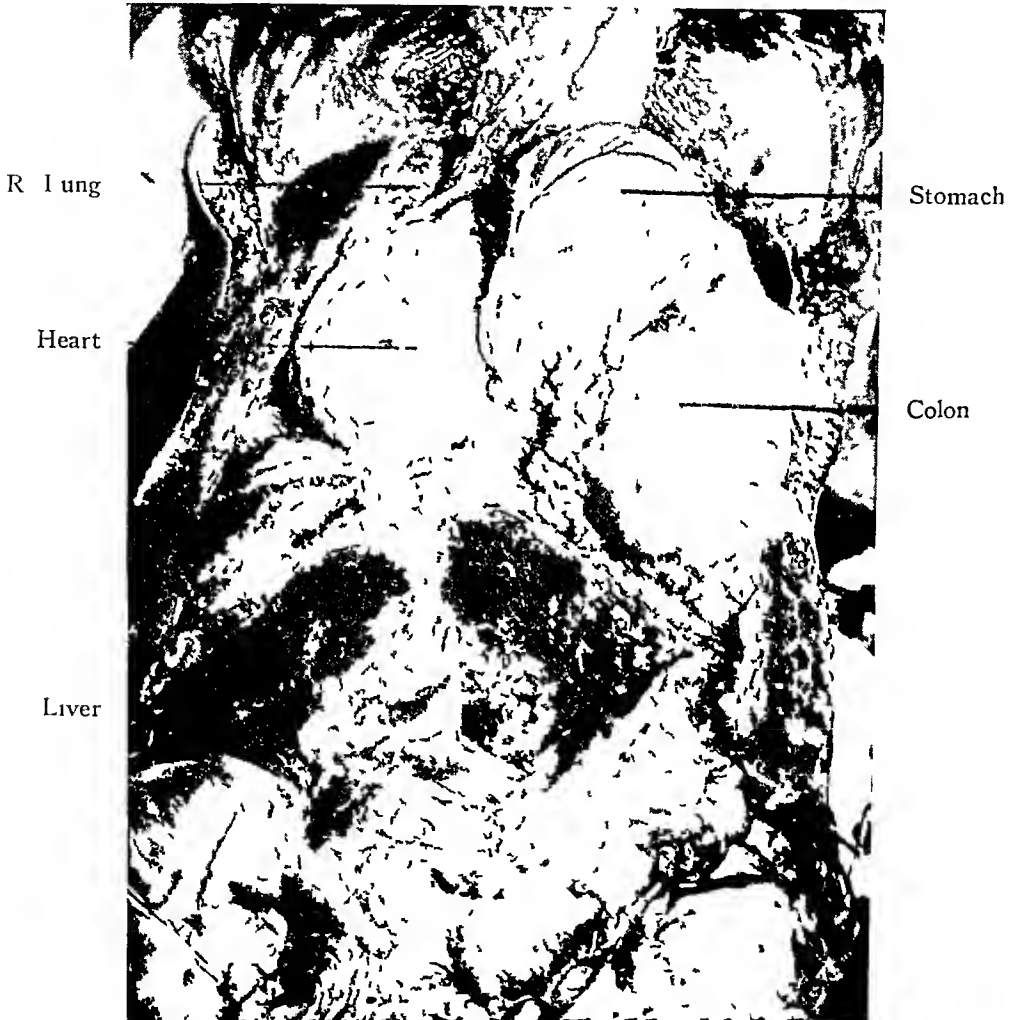


FIG 3 After removal of omentum stomach seen occupying the upper part of the left thoracic cavity, with colon below Note very small amount of lung (right), the left lung is completely collapsed

au-lait colored fluid which became thick and muddy resembling liquid feces though having no odor A second tap made anteriorly produced fluid very similar but with a definite odor of gastric contents A third tap made in the second interspace anteriorly yielded 100 c.c. air (He thought that in going so low he had introduced the needle below the level of the diaphragm into the stomach anteriorly and the large bowel posteriorly)

Postmortem Examination The autopsy summary performed by Dr Perry Hough was as follows "*General Description* There are many recent needle scars in the left chest anteriorly and posteriorly There is a two plus pitting of both legs On opening the thoracic cavity the left pleural cavity is seen to contain the entire stomach, situated in the posterior half and apical region Overlying this there are about 50 cm of transverse and descending colon with attached omentum In the left lower portion of this pleural cavity is the spleen and a portion of the tail of the pancreas is likewise included These organs have entered the left pleural cavity through a defect in the left diaphragm measuring 17 by 12 cm The edges of this defect are smooth, firm and fibrous, apparently congenital No evidence of recent laceration The left lung is completely atelectatic and contains a scar in the region of the apex suggesting an old healed pulmonary tuberculosis The heart is entirely to the right of the midline, weighs 430 grams The pericardial fluid is not remarkable There is a definite hypertrophy of the right ventricular musculature measuring on the average 11 mm in thickness The left ventricle is 19 mm in thickness There is a two plus dilatation of both ventricular cavities The myocardium everywhere appears normal and the valves are competent *Pancreas* Is of normal size On section appears quite hemorrhagic, somewhat opaque This probably represents congestion The other abdominal viscera show no gross pathology *Right Lung* Weighs 460 grams as compared to the left weighing 120 grams There is compensatory hypertrophy, especially of the upper lobes and on section a two-plus congestion No inflammatory reaction present *Microscopical Autopsy* Kidneys, spleen, pancreas and liver all show a normal microscopical structure except for a two to three plus acute passive congestion *Lungs* Moderate congestion and edema Atelectasis of left lung Section from the apical region of the left lung shows dense fibrous scar tissue with nodular areas which contain amorphous calcium deposit suggesting an old healed pulmonary tuberculosis with no evidence of activity at present *Heart* Microscopically normal"

DISCUSSION

The actions of the heart, lungs and hematopoietic system are to a considerable degree reciprocal When the surface for gaseous exchange in the lungs is markedly cut down a compensation may be partially achieved by increasing the number of erythrocytes or by increasing the rate of blood flow through the lungs In time, this will cause ventricular hypertrophy and possibly dilation as occurred in the case here reported As the distention of the stomach and colon increased, the heart was pushed so far to the right that it compressed all but the right upper lobe

SUMMARY

A fifty-year-old woman who, as far as is known, had always been in good health, entered the hospital with severe cyanosis and dyspnea after an illness of only two weeks There were no symptoms referable to the gastrointestinal tract except that she had been taking only fluids prior to admission The physical signs were those of an enormous hydrothorax on the left with displacement of the mediastinum and contents to the right The inability to obtain fluid by thoracentesis during life was surprising in view of the marked flatness but readily explainable when the true condition was revealed The aspirating needle, gently introduced in the usual manner, pushed the thick-walled viscus ahead of it and only with a vigorous thrust, after death, was the wall penetrated

Autopsy showed diaphragmatic hernia (probably congenital) with the stomach, colon and spleen and tail of the pancreas occupying the left thoracic cavity Death was apparently due to over-distention of the stomach and colon with resultant extreme anoxemia and cardiac failure

HEREDITARY DYSTROPHY OF THE HAIR AND NAILS IN SIX GENERATIONS

By HENRY JOACHIM, M D , F A C P , *Brooklyn, N Y*

IN the August 1935 issue of the *American Journal of the Medical Sciences*, M E Hobbs, of Saint John, N B, Canada, reports a case of hereditary onychial dysplasia with a genealogical chart extending to four generations including 35 members, of whom 11 were affected. I have observed a case in which this condition was accompanied by alopecia which was traced through six generations

CASE REPORT

E S, female, 24, married, French Canadian, was admitted to the Cumberland Hospital on February 11, 1935, complaining of lower abdominal pain, dysmenorrhea and backache. Since birth there was an almost complete alopecia of the scalp with absence of axillary and pubic hair. This was accompanied by deformities of the finger- and toe-nails.

*Sumner - wd 40
2-9-35*



FIG 1 Dystrophy of the finger-nails. The tunnelling of the nails is shown.

Family history A similar condition is present in her grandmother, two great aunts and mother. The patient has five brothers and two sisters who are unaffected by this abnormality. Baldness and nail deformities are recorded in six generations originating in a woman (E C) who had 10 children, five of whom had this condition (four girls and one boy). In the third generation of 10 children, three girls and two boys were affected. In the fourth generation of nine children, four girls including the patient's mother (H D) and one boy suffered from this anomaly. In the fifth generation of 11 children, three girls, including the patient (E S), were affected. In the sixth generation of two children, one girl was recorded as having this condition. The patient's mother is an epileptic, and one brother who has normal hair and nail development is mentally defective.

Past history The patient's weight at birth was three pounds. The delivery was

normal As a child she had measles and pertussis She is subject to hives from fish and oysters Her menses began at the age of 13, they were of seven days' duration until her marriage four years ago after which they decreased to four days They have occurred every 28 days and have been accompanied by lower abdominal pain and backache She suffers from leukorrhea She is sexually frigid and submits to intercourse from a sense of duty She has been pregnant on two occasions The first pregnancy was artificially terminated and was followed by sepsis The second pregnancy ended in a miscarriage following a fall The patient is subject to severe pounding temporal headaches Her vision is poor, that of the left eye being blurred since childhood She suffers from dyspnea and palpitation on exertion and since her marriage is weak and easily fatigued She is habitually constipated Within the past year she has lost 10 pounds in weight, is nervous at times and flushes easily She has had thyroid medication



FIG 2 Dystrophy of the toe-nails

Physical examination Patient is well-nourished and of fair complexion The scalp reveals a generalized alopecia with a few fine hairs varying in length from one-eighth to four inches The eyebrows are practically absent, the eyelashes are sparse Exophthalmos is present, more marked in the left eye Her skin is dry except in the axillae and palms of the hands which are moistened by perspiration A few fine hairs are present on the lips and chin Breasts, heart and lungs are negative Pulse and temperature are normal The abdomen reveals no abnormalities Vaginal examination discloses a slight discharge, cervix moderately eroded, with a tender, walnut-sized, irregular mass to the right of the uterus This mass is diagnosed as a fibroid The finger-nails are pitted and arched and convexly lifted

from the nail bed causing a tunnel-like appearance. The toe-nails are atrophic and small.

Laboratory data Roentgen-ray of the skull revealed flattening of the floor of the sella turcica. The pelvic bones were negative. Blood Wassermann test was negative. The blood sugar was 90 mg on a fasting stomach, and after a glucose tolerance test it was reported as 151.5 mg at the end of one-half hour, 121.1 mg in one hour and 119 mg after two hours. Smears from the cervix were negative for gonococci. The basal metabolic rate was minus 31. Eye examination revealed a slight uniformly contracted visual field of the left eye. The blood pressure was 100 systolic and 60 diastolic. The urine showed occasional pus cells. Hemoglobin was 90 per cent, the red cells numbered 5,160,000, and the whites 9500 with 73 per cent of polynuclears.

Therapy Patient received five injections of antuitrin S, in doses of 1 c.c. subcutaneously. This treatment was discontinued because of pelvic pain which necessitated surgical intervention. A laparotomy was performed. A right tubo-ovarian abscess and a left hydrosalpinx were found at operation. Smears and cultures from the pus were bacteriologically sterile. Convalescence was uneventful. The patient was discharged from the hospital on March 31, completely recovered from her operation.

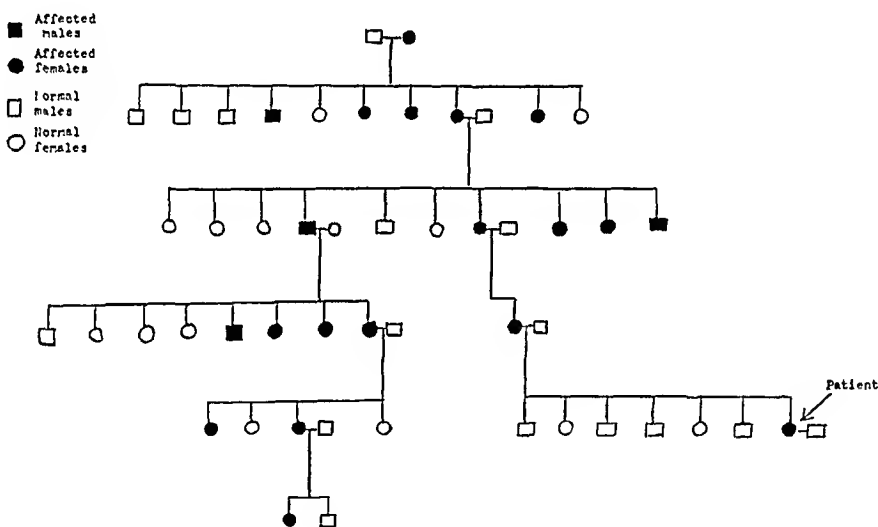


CHART I

The accompanying chart is a genealogy of the patient obtained from her mother who had in her possession a record of the family tree. No separate record is available to determine which of the cases were those of alopecia, nail deformity or both.

SUMMARY

A case of hereditary dystrophy of the hair and nails is presented. A chart is included showing the family tree of 43 members of her family with 19 suffering from this disease during a period covering six generations.

I wish to thank Dr. Walter F. Modrys, my former resident at Cumberland Hospital, for obtaining the family tree for me, and Dr. David Bellin, my present resident, for help in publishing this case.

THE NEPHROSIS SYNDROME ASSOCIATED WITH TERMINAL UREMIA

By PAUL H. WOSIKA, M.D., *Chicago, Illinois*

NUMEROUS cases of so-called "pure" "genuine" or "lipoid" nephrosis have been described in the literature. A close inspection of these reveals that very few cases in adults conform to the rigid rules clearly stated by Leiter¹ in his review of the subject in 1931. Using the clinical criteria mentioned as necessary to establish the diagnosis, several authors have published reports of groups of cases of nephrosis, whereas other authors equally interested in the problem of renal disease state that true "lipoid nephrosis" has never been observed by them. Christian² in summarizing the reported cases, was impressed by the short duration of the illness and wondered what influence the terminal infections might have had in the final pathologic picture. He was led to the conclusion that nephrosis should be regarded as one of the varieties of chronic nephritis and not as a distinct clinical entity. Using special stains in cases of clinical nephrosis, Bell³ was able to demonstrate that the chief pathologic difference that exists between glomerulonephritis and lipoid nephrosis is that in the latter "the glomerular capillaries are damaged but not completely obstructed."

The following case is reported because of the scarcity in the literature of cases which both fulfill the requirements for the clinical diagnosis of nephrosis and have been subjected to careful pathologic study. An unique feature of this patient's case was the termination in uremia which developed, under observation, without the usual elevation in blood pressure. The clinical data and sections were submitted to several pathologists specially interested in the renal problem, and their opinions and pathologic diagnoses are appended.

CASE HISTORY

E. P. F., a 25-year-old American-born housewife, entered the Peter Bent Brigham Hospital on January 27, 1933, complaining of swelling of the legs for three weeks.

The family history was irrelevant. The past history revealed that the patient had developed asthma at the age of seven years following a severe bronchitis. Intermittent attacks of severe asthma had continued thereafter. In 1927 she was admitted to the hospital because epinephrine and morphine failed to relieve an asthmatic attack. The physical examination showed emphysematous lungs and hypertrophied tonsils. Roentgenograms of the chest confirmed the clinical findings of emphysema and disclosed, in addition, a diffuse increased fibrosis at both bases. The blood Wassermann reaction was equivocally positive on two occasions. The urine examination was negative. In 1929 she was delivered normally of a male child in another hospital, but there was no record of a urine examination at that time. In 1931 the patient underwent a classical Caesarian section, at which time she was sterilized. The latter procedure was performed because chronic rheumatic heart disease with mitral stenosis had been discovered and the dependent edema that had persisted toward the end of the pregnancy was attributed to the lesion. In October

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From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Mass.
Department of Medicine, Northwestern University Medical School, Chicago, Ill.

1932, she was admitted again to the Peter Bent Brigham Hospital because of an uncontrollable attack of asthma. She was treated with epinephrine, morphine, autogenous vaccine and various barbituric acid derivatives. The blood Wassermann reactions, on three occasions, were one plus, doubtful and negative. The Hinton reaction was negative in all three instances. Lumbar puncture revealed no abnormalities of the spinal fluid.

The patient's health was fair following her discharge in October 1932, permitting her to perform her daily housework, although daily attacks of asthma necessitated epinephrine injections. Several times in the preceding five years she had noted slight edema of the ankles, and on January 5, 1933, she again noted edema of the lower extremities. On January 19, after an injection of epinephrine in her leg, she noted that fluid was escaping from the hypodermic wound in amounts sufficient to soak her stocking. The edema steadily grew more marked, and on one occasion she noted swelling of her eyelids. In addition to the edema, there was blurring of vision, spots before the eyes and marked dyspnea, but these symptoms were relieved temporarily by a watery diarrhea that followed the administration of magnesium sulphate. Thirst developed, accompanied by a decreased output of a dark colored urine. Occasional attacks of pain over the lumbar regions were relieved by hot water bags. There was a gradual but marked loss of strength. No antecedent history of upper respiratory infection could be obtained.

The physical examination on admission showed the patient to be well developed and nourished, extremely pale and markedly orthopedic. There was marked edema of the eyelids and conjunctivae. The ophthalmoscopic examination showed indistinct discs, and the surrounding fundi were pale. There were no evidences of vascular disease. The breath was bland, and there was no oral infection. The heart was slightly enlarged, and on auscultation systolic and diastolic murmurs were heard at the apex. The blood pressure was 110 systolic and 70 diastolic. Peripheral arteriosclerosis was absent. The examination of the chest showed the usual asthmatic squeaks, and there were a few coarse râles at the bases. Marked soft pitting edema was present in both legs, diminishing toward the upper thigh but present in the upper abdominal wall and back.

On admission the patient was considered to be primarily a cardiac problem because of the edema, dyspnea and findings of mitral stenosis. She was menstruating and the discovery of urinary albumin and red blood cells was ascribed to this. The underlying lesion in the kidneys was not suspected until a catheterized specimen disclosed a specific gravity of 1.045 and a very large trace of albumin, numerous casts of all descriptions and a rare red and white blood cell. A small amount of doubly refractile lipid material was detected. These urinary findings remained comparatively unchanged during the patient's two months in the hospital. The phenolsulphonephthalein dye excretion was 42 per cent after intravenous administration. The fluid intake was limited to 1000 c.c. daily, and the output was constantly around 200 c.c. in 24 hours. At the onset, the daily excretion of urinary protein was 6.1 gm. and this increased gradually to 20 gm. daily.

The total protein in the blood serum was low, and the albumin-globulin ratio was reversed (table 1). The blood cholesterol was high but decreased terminally. At first there was no appreciable retention of nitrogenous end-products but toward the end the non-protein nitrogen reached 174 mg. The first blood urea nitrogen determination was 20 mg. per 100 c.c. Three days later the non-protein nitrogen was 31 mg. per 100 c.c. The red blood count and hemoglobin determinations were normal in the beginning but diminished progressively. The blood pressure was never high and steadily decreased to questionable readings of 40 systolic and 20 diastolic. The basal metabolic rate, using the patient's ideal weight, was minus 19 per cent on two occasions. The Wassermann and Hinton reactions of the blood serum were doubtful, and no objective signs of syphilis could be found.

The patient was very cooperative, but failed to respond to the usual methods of therapy. Although she received adequate amounts of digitalis, the drug had no effect. Mersalyl (salyrgan) in 2 c c doses, given intravenously, increased the urinary output to 750 c c, 1620 c c and 1780 c c on three trials, but because of the difficulty encountered in the administration by this route, it was given intramuscularly. This proved to be very painful, and, because it resulted in a urinary output of only 970 c c, the use of this preparation was abandoned. Theophyllin (theocin) was likewise without diuretic effect. A high protein intake was attempted but not well tolerated and was without benefit. Southey tubes were used and abdominal paracenteses were performed. On one occasion 900 c c and 1075 c c of fluid were removed from the right and left pleural spaces respectively, relieving her dyspnea somewhat.

Her course in general was downhill. Four days before death she developed a pericardial friction rub. There was no fever. She became more anemic, the blood pressure decreased steadily, nitrogen retention increased, urinary protein excretion increased, the plasma carbon dioxide combining power fell to 32 volumes per cent and there was generalized twitching of the body muscles. She became comatose and died March 29, 1933, 62 days after her admission to the hospital.

The pathologic examination showed the skin to be of a waxy, livid color and pasty consistency. Anasarca was present, it was more marked in the lower extremities. The pericardial cavity contained 75 c c of a cloudy fluid with some fibrin. The pericardial surfaces were covered by numerous fibrinous adhesions.

The heart weighed 340 gm. The lesions present were limited to the mitral valve, the leaflets of which were thickened and shortened. The endocardium at the mitral valve showed a small organizing vegetation, which was interpreted as rheumatic, but which might have been an acute bacterial vegetation. A few gram-positive cocci were demonstrated in the blood clot near the vegetation but not in the fibrinous portion of it. The aorta was uniformly elastic and showed only slight fatty infiltration of the intima. There were no atheromatous plaques. The peripheral vessels were negative, and no signs of arteriosclerosis or syphilis could be found.

Microscopically, the lungs showed marked passive congestion and a patchy bronchopneumonic infiltration. Streptococci were found in the sections. The characteristic changes of asthma were minimal.

The spleen weighed 300 gm and showed evidences of edema. The microscopic changes were those of an acute splenitis. The pancreas showed acute diffuse pancreatitis with moderate acinar atrophy and fat necrosis.

The liver weighed 1950 gm and was softer than normal. It presented a brownish yellow mottled color which suggested marked fatty metamorphosis. There was moderate congestion. The liver cells, microscopically, showed marked fatty metamorphosis. These fatty deposits were mainly periportal and central in location. The portal systems were everywhere almost completely surrounded by fatty liver cells, although the elements of the portal systems were not remarkable. The liver cells in the central areas were the only ones reasonably well preserved.

The right kidney weighed 395 gm, the left 390 gm. They were of normal shape with the fetal lobulations indistinctly preserved. They were markedly swollen, very pale and of softer than normal consistency. The perirenal fat was edematous and easily removed. The capsule was thin, smooth and glistening and was not appreciably adherent. After stripping the capsule, the kidney surface was smooth. The edges tended to evert. The cortex uniformly measured 12 to 13 mm in thickness. The glomeruli did not stand out. The medullary rays were not distorted. The definition of the tubular striations was fairly well preserved, but they, too, were rather pale.

The microscopic examination of the kidneys showed edema of the capsule but no increase in fibrous tissue. There were occasional foci of lymphoid cells beneath the capsule and throughout the renal parenchyma, but there was no accom-

panying necrosis of tissue. Migrating polymorphonuclear leukocytes were scattered throughout the interstitial tissues. There was a marked generalized edema and a distinct interstitial fibrosis. The afferent vessels showed no sclerosis, and none were completely or partially occluded. The glomerular tufts were quite bloodless and shrunken, and the capillaries showed no endothelial proliferation. There was a slight hyalin thickening of the basement membranes. There were no atrophic or hyalinized glomeruli, but rarely a glomerulus showed some capsular proliferation and capsular adhesion. The glomeruli appeared surprisingly normal, and on the whole, the renal tissue was fairly well preserved. Characteristic changes of an acute or chronic glomerulonephritis were absent. The tubules were dilated. They contained an unusual amount of albuminous precipitate and numerous hyalin and cellular casts. The tubular epithelium had an unusually high fat content. Fat was largely present in the cells and lumina of the convoluted tubules. Vacuolization and colloid degeneration were prominent throughout. Flattened, cuboidal, regenerated tubular lining cells were common. Necrosis and desquamation of epithelium were noted in many fields.

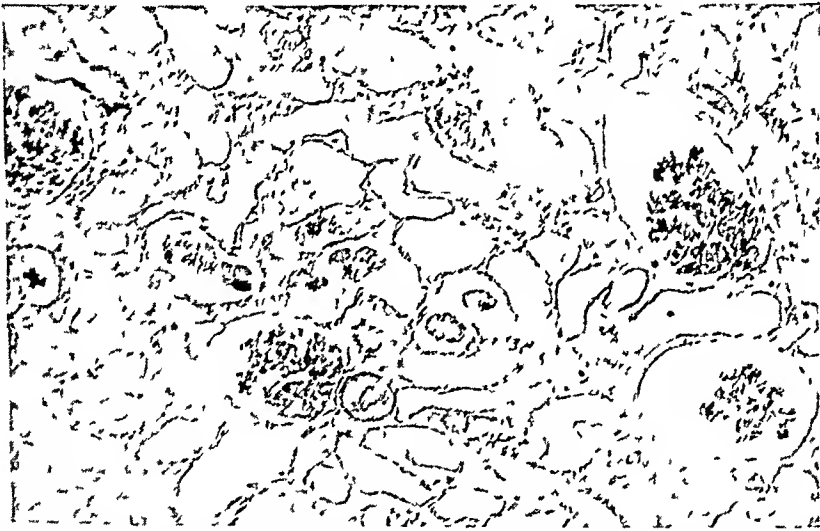


FIG 1 Section of the kidney (H and E stain, magnified 95 times) showing the bloodless and shrunken glomerular tufts, interstitial edema and fibrosis, dilated tubules containing albuminous precipitate and hyalin and cellular casts

The arteries showed no sclerosis and none were occluded. There was no passive congestion. The interlobar veins were almost completely occluded bilaterally by thrombi. The thrombi contained slightly hyalinized strands of fibrin and entrapped leukocytes. In one kidney a thrombus showed early organization. The thrombi were interpreted as being of recent origin because they were, for the most part, unorganized. The renal parenchyma showed no hemorrhagic necrosis.

Special stains of the kidney, such as phosphotungstic acid hematoxylin, Lee Brown, aniline blue and Scharlach R, contributed little to the histologic study. None demonstrated any significant glomerular changes. Dr S B Wolbach was impressed by the interstitial edema, interstitial fibrosis, the diminution in the number of capillaries between the tubules and the slight focal interstitial round cell infiltration. These changes with the tubular vacuolization and fatty metamorphosis constituted the outstanding changes in the kidneys.

Blood cultures and cultures from the kidney were negative.

Anatomic Diagnoses Tubular nephritis (lipoid nephrosis), thrombosis of interlobar veins. Vegetative endocarditis of the mitral valve, mitral stenosis and insuf-

iciency Pericarditis, fibrinous, bronchopneumonia (right, acute) Passive congestion of viscera, anasarca, ascites (750 cc), hydrothorax, bilateral, hydropericardium (75 cc) Pancreatitis with fat necrosis (acute) Fatty metamorphosis, liver, marked Occlusion Fallopian tubes (post-operative)

COMMENT

No history of an inciting infection could be obtained in this case. Because of the numerous entrances into the hospital, repeated Wassermann reactions were on record, and every effort was made to establish syphilis as the etiologic agent. At no time, however, could the Wassermann reaction be considered to be positive, and no stigmata of this disease could be found. No reason for the many weakly positive reactions could be ascertained. The absence of a chronic wasting disease made amyloidosis seem unlikely. The postmortem examination confirmed the absence of these factors. In addition, there was no association with the previous pregnancies that could be traced.

The onset of the disease definitely occurred within the three months' period following the previous hospital admission, but was so gradual that the patient's complaints dated from the time that the massive edema was present. The whole picture was complicated by the long standing chronic rheumatic heart disease and asthma. These, however, did not contribute to the patient's death.

Clinically, shortly after admission, this patient was considered to be a well marked case of the nephrosis syndrome. The scant initial elevation of the blood urea nitrogen had been noted, and three days after admission the non-protein nitrogen was normal. The lack of response of this patient to the usual therapeutic procedures was no surprise. However, with the development of the azotemia that steadily grew more pronounced, the glomeruli were visualized as undergoing marked pathologic change, another example, then, of nephrosis developing terminally into glomerulonephritis.

Pathologically, however, the kidneys were, in every respect, typical of the so-called "pure," "genuine" or "lipoid" nephrosis. The tubules showed the characteristic degenerative lesions. The glomeruli, while not normal, could not be considered to be characteristic of those usually seen in glomerulonephritis. Evidences of a blood stream infection were noted, which had been unsuspected clinically. There had been no fever. The exact nature of this bacterial invasion could not be determined with certainty, but the belief that it was streptococcal was based upon the finding of these organisms in the clots along the mitral valve, the typical streptococcal patchy bronchial pneumonia and the demonstration of these organisms in the microscopic sections of the lungs and the inflammatory lesions of the pancreas and spleen. The negative blood cultures cannot rule out the presence of this terminal septicemia.

The unusual thromboses observed in the renal veins were recent in origin and the part played by these lesions in the uremia cannot be answered with any degree of surety. However, these lesions probably played a part in hastening the end rather than initiating the onset of the uremia.

Because of our inability to state with certainty the factors leading to the fatal uremia and their relative importance, we submitted the slides together with the clinical history to several well-known pathologists interested in the renal problem. The following courteous and interesting replies were made independently, are illuminating and require no further comment.

(1) One stated, "From the history and the slides, this seems to me to be unequivocally a case of chronic nephrosis ('lipoid nephrosis')"

(2) Another considered the clinical and pathological aspects as representing nephrosis or degenerative Bright's disease. The microscopic study, according to him, shows the kidney to be characterized by edema, tubular epithelial atrophy and degeneration and a heavy precipitate of protein and casts within the tubules. The extreme degree of edema and precipitated protein and casts gives the striking microscopic appearance. The venous thrombi were considered to be a possible explanation for the unusual histologic appearance even with the lack of passive congestion present, and the increase in venous pressure may have borne some relation to the edema of the kidney tissue.

(3) Still another considered the case as one of severe toxic nephrosis, not "lipoid", and suggested morphine as the toxic agent since it can produce a similar picture in susceptible individuals. (Although we administered morphine frequently and freely, we could not gather evidence pointing to a chronic morphine addiction nor to the possibility of a supply other than what she received at our hands for the treatment of the asthma. According to the records, morphine was first administered in 1927. During her last hospital admission, morphine or codeine was given from one to three times daily.)

(4) Another wrote, "The kidney shows glomeruli which are typical of chronic lipoid nephrosis. The glomeruli show narrow capillaries, the narrowing being due, for the most part, to thickening of the capillary basement membrane. The tubules contain a large amount of precipitated albumin and a great many casts. The dilatation of the tubules may be due to obstruction by the casts. In this particular case the marked renal insufficiency that developed is probably caused by obstruction of the tubules by casts. This feature is not seen usually in lipoid nephrosis, but I have seen one case with a similar obstruction resulting in uremia. If the casts were not present a kidney in this condition would show only a moderate nitrogen retention. The clinical picture corresponds to what one would expect from the anatomic changes except that, as a rule, the blood pressure is elevated with this type of renal lesion."

"In studying a large group of cases of glomerulonephritis a great variety of structural changes is found and it is not possible to separate sharply the types due to endothelial proliferation from those due to thickening of the basement membrane. In many cases both the basement membrane and the endothelium take part in the capillary obstruction. There is, however, a fairly large group of cases which resemble this one in that the chief obstruction is due to thickening of the basement membrane. Personally, I do not believe that lipoid nephrosis is sharply separable from other forms of glomerulonephritis, but those in which the basement membrane of the glomerular capillaries is prominently involved usually give a story as is present in your case."

(5) Another wrote, "The marked albuminuria indicates that the glomeruli were hyperpermeable in spite of the absence of demonstrable changes in the majority of them. The arterioles were likewise free from change. The retention of nitrogenous waste products must have been due, therefore, to some cause outside the glomeruli and blood vessels. One or more of the following factors may have been responsible — (1) The diversion of water into the tissues caused the marked oliguria. The output of urine may have been insufficient even when greatly concentrated, to excrete a sufficient amount of urea. The

importance of this factor in this case can be determined in some measure by the effect of mersalyl on blood urea (2) Edema of the interstitial tissue of the kidney was of sufficiently high degree to cause considerable increase in intrarenal pressure with interference with the renal circulation The fact that the glomeruli were practically bloodless, in spite of the obstruction (thrombosis) in the renal veins, suggests that this was an important factor in the retention (3) Plugging of the tubules with casts was of sufficient extent to be included among the possible factors in causing retention In my opinion, increased intrarenal pressure due to edema of the kidneys themselves and oliguria due to diversion of water into the tissues are the most important of the factors mentioned

"In my opinion, this is a case of glomerulonephritis for the following reasons (1) A limited number of glomeruli did contain epithelial crescents or adhesions between the glomerular tufts and the capsule of Bowman (2) Occasional foci of lymphocytic infiltration were present in the sections (3) The presence of casts in such enormous numbers would seem to exclude this case rather definitely from the category of nephrosis (4) Although the cholesterol of the blood was increased, the degeneration of the tubular epithelium was said to be fatty instead of lipoidal"

SUMMARY

A woman, 25 years of age, developed the clinical picture of nephrosis typical in all respects except a slight questionable nitrogen retention which became marked terminally without, however, the expected rise in blood pressure Death occurred after 62 days of careful observation in the fifth month of the disease Postmortem evidence was found of a terminal, probably streptococcal, general infection

The kidneys showed tubular changes characteristic of nephrosis with glomerular damage minimal or almost entirely absent The various interpretations of competent pathologists especially interested in the renal problem illustrate the confusion surrounding the subject of nephrosis In the case reported the microscopic picture commonly considered typical of nephrosis was associated with clinical findings (azotemia) usually produced by a form of glomerulonephritis

It would seem that the word nephrosis should be restricted to a convenient term for a clinical syndrome rather than be used as a descriptive of a pathologic entity

I am deeply grateful to Drs H A Christian and J P O'Hare, on whose service this case was seen, for permitting its publication, to Drs S B Wolbach, J P Simonds, W H Nadler, and M H Barker for their many valuable criticisms and suggestions and to Miss Margaret Driscoll who performed the chemical determinations My thanks are also due the pathologists who were kind enough to review the case and submit to me their opinions

REFERENCES

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- 2 CHRISTIAN, H A Nephrosis a critique, Jr Am Med Assoc, 1929, xciii, 23
- 3 BELL, E T Lipoid nephrosis, Am Jr Path, 1929, v, 587

EDITORIAL

THE AMERICAN BOARD OF INTERNAL MEDICINE

The American Board of Internal Medicine incorporated February 28, 1936, completed its organization on June 15, 1936. The officers chosen were Walter L. Bierring, M D, Des Moines, chairman, Jonathan C. Meakins, M D, Montreal, vice-chairman, and O. H. Perry Pepper, M D, Philadelphia, secretary-treasurer. These officers with the following six members constitute the present membership of the Board: David P. Barr, M D, St. Louis, Reginald Fitz, M D, Boston, Ernest E. Irons, M D, Chicago, William S. Middleton, M D, Madison, John H. Musser, M D, New Orleans, and G. Gill Richards, M D, Salt Lake City.

The term of office of each member shall be three years and no member shall serve more than two consecutive three-year terms.

The organization of the Board is the result of effective effort on the part of the American College of Physicians in conjunction with the Section on Practice of Medicine of the American Medical Association, and these two organizations are represented in the membership of the Board on a five to four ratio respectively.

The American Board of Internal Medicine had previously received the official approval of the two bodies fostering its organization, as well as that of the Advisory Board for Medical Specialties and the Council on Medical Education and Hospitals of the American Medical Association.

The purpose of the Board shall be the certification of specialists in the field of internal medicine, and the establishment of qualifications with the required examination procedure for such certification.

The value of such certification can be stated as (1) an attest of special training and qualification for the practice of internal medicine as a specialty, (2) registration with proper designation in the directory of the American Medical Association, and (3) the certificate will constitute an essential requirement for election to Fellowship in the American College of Physicians.

While the Board is at present chiefly concerned with the qualification and procedure for certification in the general field of internal medicine, it is intended to inaugurate immediately after July 1, 1937, similar qualification and procedure for additional certification in certain of the more restricted and specialized branches of internal medicine, as gastroenterology, cardiology, metabolic diseases, tuberculosis, allergic diseases, et cetera. Such special certification will be considered only for candidates who have passed at least the written examination required for certification in general internal medicine. The operation of such a plan will require the active participation and cooperation of recognized representatives from each of such special fields of medicine.

Each applicant for admission to the examination in internal medicine will be required to meet the following standards

General Qualifications

- 1 Satisfactory moral and ethical standing in the profession
- 2 Membership in the American Medical Association or, by courtesy, membership in such Canadian or other medical societies as are recognized for this purpose by the Council on Medical Education and Hospitals of the American Medical Association Except as here provided, membership in other societies will not be required

Professional Standing

- 1 Graduation from a medical school of the United States or Canada recognized by the Council on Medical Education and Hospitals of the American Medical Association
- 2 Completion of an internship of not less than one year in a hospital approved by the same Council
- 3 In the case of an applicant whose training has been received outside of the United States and Canada, his credentials must be satisfactory to the above Council, the Advisory Board for the Medical Specialties and the National Board of Medical Examiners

Special Training

- 1 Five years must elapse after completion of a year's internship in a hospital approved for intern training, before the candidate is eligible for examination
- 2 Three years of this period must be devoted to special training in Internal Medicine This requirement should include a period of at least several months of graduate work under proper supervision in Anatomy, Physiology, Biochemistry, Pathology, Bacteriology, or Pharmacology, particularly as related to the practice of Internal Medicine, or it may include a period of at least several months of graduate work under proper supervision in Internal Medicine or in its restricted and specialized branches This graduate work may be carried on in any domestic or foreign medical school, laboratory, hospital, clinic or dispensary, recognized by the Council on Medical Education and Hospitals of the American Medical Association as offering appropriate facilities for this type of postgraduate experience
- 3 A period of not less than two years of special practice in the field of Internal Medicine, or in its more restricted and specialized branches

The American Board of Internal Medicine does not propose to establish fixed rules for the preliminary training of candidates for certification in this field Broad general principles for training, however, may be outlined, although such suggestions as are

made must of necessity be subject to constant changes reflecting the dynamic nature of the specialty

A sound knowledge of Physiology, Biochemistry, Pharmacology, Anatomy, Bacteriology, and Pathology in so far as they apply to disease is regarded as essential for continued progress of the individual who practices Internal Medicine. The mere factual knowledge of Medicine and its basic sciences is not sufficient. The candidate must have had training in their use in furthering his understanding of Clinical Medicine. This implies practical experience under the guidance of older men who bring to their clinical problems ripe knowledge and critical judgment. Preparation to meet this requirement adequately may be even more difficult to obtain than the so-called scientific training. It may, however, be acquired in the following ways

- (a) By work in a well-organized Hospital Out-Door Clinic conducted by competent physicians,
- (b) By a prolonged period of resident hospital appointments likewise directed by skilled physicians,
- (c) By a period of training in intimate association with a well-trained and critical physician who takes the trouble to teach and guide his assistant rather than to require him only to carry out the minor drudgery of a busy practice

- 4 The Board does not consider it to the best interests of Internal Medicine in this country that rigid rules as to where or how the training outlined above is to be obtained. Medical teaching and knowledge are international. The opportunities of all prospective candidates are not the same. Some may have the opportunity of widening their knowledge by a period of study abroad. Others, at the other extreme, may be restricted to a comparatively narrow geographic area and their more detailed training must be obtained in short periods scattered over a longer time. Although it is laid down that at least five years must elapse between the termination of the first intern year, and when the candidate is eligible to take the examination, a longer time is advisable. The Board wishes to emphasize that the time and training are but a means to the end of acquiring a broadness and depth of knowledge of Internal Medicine which the candidate must demonstrate to the Board in order to justify it in certifying that he is competent to practice Internal Medicine as a specialty. The responsibility of acquiring the knowledge as best he may rests with the candidate, while the responsibility of maintaining the standard of knowledge required for certification devolves on the Board.

Method of Examination

The examination required of candidates for certification as specialists in Internal Medicine will comprise Part I (written), and Part II (practical) or (clinical)

Part I The written examination is to be held simultaneously in different centers of the United States and Canada and will include

(a) Questions in applied Physiology, Physiological Chemistry, Pathology, Pharmacology, and the cultural aspects of medicine

(b) Questions in general Internal Medicine

The first written examination will be held in December, 1936, and candidates successful in this written test will be eligible for the first practical or clinical examination which will be conducted by members of the Board near the time of the annual session of the American College of Physicians at St. Louis in April, 1937. Another written examination will be held in February, 1937, followed by a practical test in Philadelphia in June, 1937.

The fee for examination is forty dollars which must accompany the application, and an additional fee of ten dollars is required when the certificate is issued.

Application blanks and further information can be obtained by addressing the office of the chairman, Room 1210, 406 Sixth Avenue, Des Moines, Iowa, U. S. A. The organization of the American Board of Internal Medicine is largely due to the initiative of the American College of Physicians, and as such, will be regarded one of its most worthwhile accomplishments.

The certification procedure will distinctly influence the Standards of Fellowship in the College and likewise be a motive force towards higher ideals of internal medicine in America.

REVIEWS

Fundamentals of Biochemistry in Relation to Human Physiology By T R PARSONS
Fifth Edition 453 pages, 13 × 19 cm Wm Wood and Co, Baltimore 1935
Price, \$3 00

This is the fifth edition of this work, which first appeared in 1923, and which has retained an undiminished and deserved popularity ever since. The author's style is clear and lucid and he has succeeded in meeting the needs of those with a minimum of previous knowledge of pure chemistry and physics. In this edition he has kept step with important chemical advances of practical interest. At the end of each chapter is a well selected bibliography for further reading. No doubt this is one of the best books now available which embraces within a reasonable compass and in a clear and simple manner most of the important information which the well informed practitioner requires in this field.

G A H

Immunology By NOBLE PIERCE SHERWOOD, Ph D, M D, Professor of Bacteriology, University of Kansas, and Pathologist to The Lawrence Memorial Hospital, Lawrence, Kansas 608 pages, 16 × 23.5 cm C V Mosby Company, St Louis 1935 Price, \$6 00

The preparation of this book has resulted from the author's experience in the teaching of immunology to medical students and the college students whose major work has been in bacteriology. It has been written primarily for them rather than for those intending to specialize in immunology. Sherwood has attempted to present this science in such a manner as to induce the student to correlate with it some of his knowledge of other subjects and to utilize this knowledge in the explanation both of infection and resistance and of the various serologic procedures. The practical application of these procedures is also discussed. In general the subject is well presented but at times the discussion is rather brief. There is, however, a good list of references at the end of each chapter for the use of the student who wishes more detailed information about some particular phase of immunology. This book should be of value to those for whom it has been written.

F W H

The Balanced Diet By LOGAN CLENDENING, M D 207 pages, 13 × 19 cm D Appleton-Century Co, New York 1936 Price, \$1 50

This is another of the group of low-priced books on diet and allied subjects for popular consumption which have appeared in increasing numbers this year. The author is well known for his syndicated press articles on medical topics, and the book is written in a popular, informal style. There is some fresh historical material upon dietetics which is of interest. The publishers have included some extraordinarily crude sketches illustrating the plight of unfortunates with various vitamin deficiencies.

The advisability of including the chapter on Diet in Disease in a book of this type is at least debatable. There is an interesting discussion of food fads. At the back the book is provided with the customary food tables and other similar data.

G A H

A Handbook of Urology By VERNON PENNELL 224 pages, 13 × 19 cm The Macmillan Company, New York 1936 Price, \$2.75

This small handbook represents an attempt to place in the hands of students and practitioners a simple outline of the facts which must be accumulated and evaluated in the process of reaching a diagnosis in the field of urology. It contains much of value. The chapter on genito-urinary tuberculosis is of especial interest. On the other hand it seems open to criticism that a discussion of the venereal diseases is not included. Moreover, in view of the object of the book there is a disproportionate amount of space devoted to description of operative procedure and not enough consideration of pathology and of diagnosis.

W H T

New Pathways for Children with Cerebral Palsy By GLADYS GACE ROGERS and LEAH C THOMAS 167 pages, 14 × 20.5 cm The Macmillan Company, New York 1935 Price, \$2.50

The practical management of cerebral spastic palsy has always been difficult due to the medical condition of the patient, the psychological reaction of the parents and the few therapists available with a suitable attitude toward and aptitude for the very slow and complicated procedures. The authors have presented most completely and thoroughly the principles of treatment which have been known but which have never been well coordinated. The book is very interestingly written so that even the technical angles will be understood by the average layman.

All the various types of apparatus employed are so simple that they can be duplicated in the home, and their use is easily understood. The extensive and variable list of games and methods of developing mental and physical coordination will be of tremendous aid to technicians, parents and clinicians.

Of particular interest is the chapter entitled "Responsibilities of the Parents" which briefly but forcibly states the essentials of proper care of the spastic child in the home. "Robin Hood's Barn" must be a most fascinating and interesting place.

The appendix offers a simple but accurate record system for recording improvement changes. The bibliography is broad and complete. The reviewer believes that this book is an important addition to the literature of cerebral palsy. It covers a field generally neglected by the medical profession. It is recommended to physicians and parents.

A V

Allergy of the Nose and Paranasal Sinuses A Monograph on the Subject of Allergy as Related to Otolaryngology By FRENCH K HANSEL, M D, M S 820 pages, 18.5 × 26 cm, with 58 illustrations and 3 color plates C V Mosby Co, St Louis, Mo 1936 Price, \$10.00

The title of this work suggests that its scope is rather narrow, limited to a discussion of allergic manifestations in the nose and sinuses. The secondary title expresses more adequately its completeness. Fifteen of the 35 chapters are devoted to the nose and sinuses, 20 to the subject of allergy in general, without specific reference to the upper respiratory tract.

The author has assembled and organized a great mass of information on the physiology, biochemistry, cellular reactions, and bacteriology of the nose and paranasal sinuses, in the normal, allergic and infected states. The discussion of the effect of drugs on nasal physiology is interesting and important, as it emphasizes the harmfulness of certain local applications commonly used in the nose. The chapter on histology and histopathology is fully illustrated.

Chapters VIII to XV review the subject of allergy in general. The origin and development of our concept of allergy, history taking and methods of testing, are fully and clearly presented, without the confusion frequently seen in writings on this subject.

Chapters XVI to XX discuss the nasal manifestation of allergy, the cytology of the nasal secretions, differential diagnosis and sinus complications in allergy, with one chapter on the roentgen-ray examination of the sinuses. Other chapters on urticaria, headache, bronchial asthma, bronchoscopy, allergic lesions of the ear, and allergy and immunology in ophthalmology round out the work. Chapter XXX, on treatment, is very complete.

The final chapters are devoted to the subject of hay fever, botany and geography of offending plants, chemistry, immunology, symptomatology, diagnosis, and treatment of hay fever.

The reviewer feels that this book is a valuable contribution. The literature is covered fully, digested well and presented clearly. It is certainly a most complete work on an important subject.

T N C

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following gifts to the College Library of publications from members

Dr Frederick T Lord (Fellow), Boston, Mass—1 autographed book, "Lobar Pneumonia and Serum Therapy",

Dr Herman O Mosenthal (Fellow), New York, N Y—1 autographed book, "The Diagnosis and Treatment of Variations in Blood Pressure and Nephritis",

Dr Julius P Dworetzky (Fellow), Liberty, N Y—1 reprint,

Dr Norbert Enzer (Fellow), Milwaukee, Wis—14 reprints,

Dr Marjorie E Reed (Fellow), Plymouth, Pa—3 reprints,

Dr Ramon M Suarez (Fellow), San Juan, P R—1 reprint

Dr Jacob Gutman (Fellow), Brooklyn, N Y—"Seventh Supplement to 'New Modern Drugs'",

Dr Philip B Matz (Fellow), Washington, D C—1 reprint,

Dr Jacob Greenstein (Associate), Providence, R I—1 reprint,

Dr John S Hibben (Associate), Pasadena, Calif—1 reprint,

Dr Bert F Keltz (Associate), Oklahoma City, Okla—1 reprint

WASHINGTON ACADEMY OF MEDICINE

The Washington Academy of Medicine, Washington, D C, has been organized with a membership limited to 60, of whom one-half must be non-medical men but workers in medical science. It is one of the objects of the Academy to bring such men and such physicians more closely together. Dr William A White (Fellow) is President. In addition to Dr White, among the Charter members, appear the following Fellows of the College

Dr Walter A Bloedorn

Dr Walter Freeman

Dr Edgar E Hume

Dr George W McCoy

Dr Earl B McKinley

Dr William J Mallory

Dr Matthew W Perry

Dr Charles R Reynolds

Dr Perceval S Rossiter

Dr Joseph F Siler

Dr Walter L Treadway

Among its medical members also are 11 Fellows of the American College of Surgeons

ALPHA GAMMA MU ALPHA

A new organization Alpha Gamma Mu Alpha, a postgraduate medical fraternity, was formed at Kansas City during the last meeting of the American Medical Association. The stated object of this Society is "to promote thought". There are no dues, and the initiation fee is one dollar. Meetings will be held when and where the American Medical Association meets. Members must belong to their County and State Medical Societies and the American Medical Association. Dr Arthur E Guedel, Beverly Hills, Calif, is President, Dr LeRoy S Peters (Fellow), Albuquerque, N M, is Secretary-Treasurer, and Dr John W Shuman (Fellow), Los Angeles, Calif, is Delegate.

Dr Charles J Bloom (Fellow), New Orleans La, as a faculty member of the Southern Pediatric Seminar, lectured and conducted clinics on July 27 through August 2, inclusive, at Saluda, N C

Dr Bloom participated in the Postgraduate Course, July 6 to 18, incl, of the Flint-Goodridge Hospital of Dillard University

He also conducted a pre-school clinic in Bay St Louis, Miss, June 19, sponsored by the Parent-Teachers' Association U S Public Health Service and the physicians of Harrison County, Miss

Dr George M Decherd, Jr (Associate), formerly Instructor in Medicine at the University of Texas School of Medicine, Galveston, has accepted an appointment as Assistant Professor in the Department of Medicine of Louisiana State University, New Orleans, his appointment taking effect as of July 1, 1936

The fifty-sixth annual meeting of the Lehigh Valley Medical Association was held at Pocono Manor, Pa, July 15, under the presidency of Dr J K Williams Wood (Associate), Willow Grove, Pa

Dr John H Musser (Fellow), New Orleans, Professor of Medicine at Tulane University of Louisiana School of Medicine, was the guest speaker, his subject being "Abdominal Pain Due to Extra-Abdominal Disorders"

Major General Charles R Reynolds (Fellow), Surgeon General of the U S Army, received the honorary degree of Doctor of Science from Dickinson College, Carlisle, Pa, in June

Dr William G Herrman (Fellow), Asbury Park, N J, has been elected a Vice-President of the Medical Society of the State of New Jersey

Dr Joseph Frederick Panton (Fellow), Buffalo, has received the appointment of Associate in Medicine at the University of Buffalo School of Medicine

Dr Isidore W Held (Fellow), New York City, has been appointed Clinical Professor of Medicine at the New York University College of Medicine

Dr Chester W Waggoner (Fellow), Toledo, Ohio, has been appointed a member of the Ohio State Medical Board for a term of seven years

Dr Edward H Schwab (Fellow), Galveston, has been elected President of the Texas State Heart Association, Dr Robert M Barton (Fellow), Dallas, was elected Secretary

Dr Frank C Hodges (Fellow), Huntington, W Va, has been elected a Vice-President of the West Virginia Medical Association Dr Hodges delivered the annual oration in medicine, "The Diagnostic Value of Intradermal Injections," at the State meeting held in Fairmont, June 8 to 10

Dr Walter M Simpson (Fellow), Dayton, Ohio, is Chairman of the American Committee for the First International Congress on Fever Therapy, which was to have been held in September, but has now been postponed until March 30 to April 2, 1937 The sessions will be held at the College of Physicians and Surgeons of Columbia University, New York City

Dr Francis M Pottenger (Fellow), Monrovia, Calif, has been elected President of the American Association for the Study of Internal Secretions

Dr Hugh S Cumming (Fellow), formerly Surgeon General of the U S Public Health Service, has been elected President of the Pan-American Conference of National Directors of Health

Dr William S Middleton (Fellow), Dean of the University of Wisconsin Medical School, Madison, delivered the first Harry A Sifton Memorial Lecture at the Milwaukee Hospital, May 21, on "The Tools with Which We Work"

Dr T M Durant (Associate), formerly of Tucson, Ariz, has been appointed Assistant Professor of Internal Medicine at Temple University School of Medicine, Philadelphia, Pa, effective August 1

Dr Lewis H Hitzrot (Associate), formerly of Philadelphia, has accepted the Medical Directorship of the Meicersburg Academy, Meicersburg, Pa, effective September 1

Dr Langley Porter (Fellow), San Francisco, has retired as Dean of the University of California Medical School, but will continue his affiliation with an emeritus status as an adviser in administration and research Dr W McKim Marriott (Fellow), St Louis, succeeds Dr Porter as Dean

Dr Henry A Christian (Fellow), Hersey Professor of Theory and Practice of Physic, Harvard University Medical School, will deliver the third Frank Billings Lecture of the Thomas Lewis Gilmer Foundation before a joint meeting of the Institute of Medicine of Chicago and the Chicago Society of Internal Medicine, October 26, on "Edema, Diuretics, Diuresis"

Dr Leo Loeb, Edward Mallinckrodt Professor of Pathology, Washington University School of Medicine, St Louis, and the 1935 John Phillips Memorial Medalist of the American College of Physicians, has announced his retirement at the end of this year

Dr Matthew Shapiro (Associate), New York City, represents Internal Medicine in a group of physicians appointed by the Board of Directors of the Associated Hospital Service of New York to serve in an advisory capacity, especially regarding the eligibility of subscribers to services under the hospital plan

Dr Cecil Striker (Fellow), Cincinnati, Ohio, has been appointed Chairman of a special committee on diabetes formed by the Public Health Federation of Cincinnati, in cooperation with the Academy of Medicine of Cincinnati The Committee will establish a bureau of information for physicians and the public, to carry on a study of the morbidity and mortality of diabetes and to promote public health education concerning the treatment of diabetes

AMERICAN COLLEGE OF PHYSICIANS

Geographical Distribution of Members

August 6, 1936

United States	Associates	Fellows	Masters	Total
Alabama	9	16		25
Arizona	2	26		28
Arkansas	5	19		24
California	39	201		240
Colorado	17	43		60
Connecticut	17	54		71
Delaware	1	7		8
District of Columbia	30	99		129
Florida	6	25		31
Georgia	15	45		60
Idaho	2	1		3
Illinois	35	116	1	152
Indiana	12	32		44
Iowa	14	32		46
Kansas	11	14		25
Kentucky	13	37		50
Louisiana	10	43		53
Maine	3	18		21
Maryland	17	60		77
Massachusetts	27	92		119
Michigan	49	126		175
Minnesota	15	96		111
Mississippi	5	12		17
Missouri	9	65		74
Montana	1	10		11
Nebraska	17	31		48
Nevada		2		2
New Hampshire	2	6		8
New Jersey	18	76		94
New Mexico	2	12		14
New York	109	319		428
North Carolina	14	55		69
North Dakota	1	6		7
Ohio	52	103		155
Oklahoma	18	28		46
Oregon	9	17		26
Pennsylvania	89	228	2	319
Rhode Island	8	11		19
South Carolina	7	11		18
South Dakota	4	3		7
Tennessee	10	37		47
Texas	36	77		113
Utah	2	4		6
Vermont	1	2		3
Virginia	17	44		61
Washington	11	23		34
West Virginia	16	29		45
Wisconsin	6	47		53
Wyoming		1		1
U S Possessions				
Canal Zone	3	10		13
Hawaii	1	8		9
Philippine Islands	1	5		6
Puerto Rico	8	5		13
Total (U S & Possessions)	826	2489	3	3318

TABLE—*Continued*

United States	Associates	Fellows	Masters	Total
Canada				
Alberta		1		1
Manitoba	1	2		3
New Brunswick		1		1
Ontario	10	29		39
Quebec	4	14	1	19
Saskatchewan		1		1
Central America	3	1		4
Channel Islands		1		1
China	1	6		7
Colombia		1		1
England		1		1
France		1		1
India	1			1
Mexico		5		5
Panama	1	3		4
Romania		1		1
Siam		1		1
Syria		1		1
GRAND TOTAL	847	2559	4	3410

Dr Francis G Blake (Fellow), Sterling Professor of Medicine, Yale University, New Haven, was awarded the honorary degree of Doctor of Science by Dartmouth College at the past June commencement

Dr John Walker Moore (Fellow), Dean of the University of Louisville School of Medicine, has been given the University 1936 Award of Merit. From his citation, the following is quoted: "significant contribution through research on cardiovascular functions, establishment a decade ago of the student unit system of clinical instruction, effective and stimulating teaching." Dr Moore has been on the faculty of the University since 1915, having been Professor of Medicine since 1923 and Dean since 1928. He is a graduate of the University of Pennsylvania School of Medicine, 1912.

Dr William B Castle (Fellow and John Phillips Memorial Award Medalist, 1933, of the American College of Physicians) has recently been awarded the honorary degree of Doctor of Medicine by Utrecht University.

Dr Martha Tracy (Fellow), Dean of the Woman's Medical College of Pennsylvania, has resumed active duty after a year's leave of absence.

Dr Charles W Burr (Fellow), Philadelphia, has been appointed, by Mayor Wilson, a member of the advisory staff to supervise treatment of patients at the Philadelphia Hospital for Mental Diseases at Byberry.

Dr Martin E Rehfuess (Fellow), Dr Henry K Mohler (Fellow), and Dr Baldwin L Keyes (Associate), all of Philadelphia, have been advanced by Jefferson

Medical College to Professor of Clinical Medicine, Clinical Professor of Therapeutics and Clinical Professor of Psychiatry, respectively

Sir Frederick Banting (Fellow), Professor of Medical Research at the University of Toronto, has been elected to Fellowship in the Royal College of Physicians, London

Dr William Devitt (Fellow), Allenwood, Pa., has been reelected President of the Federation of American Sanatoria

CIRCULATION

Annals of Internal Medicine (Vol IX, No 12, June, 1936)

<i>Middle Atlantic States</i>		<i>Western States</i>	
Delaware	10	Arizona	30
Dist of Columbia	126	California	252
Maryland	85	Colorado	57
New Jersey	112	Idaho	4
New York	480	Montana	14
Pennsylvania	368	New Mexico	13
Virginia	63	Nevada	2
West Virginia	45	Oregon	27
		Utah	7
	1289	Washington	40
<i>Central States</i>		Wyoming	1
Illinois	167		447
Indiana	50	<i>New England States</i>	
Iowa	47	Connecticut	76
Kansas	30	Maine	21
Kentucky	47	Massachusetts	131
Michigan	195	New Hampshire	8
Minnesota	113	Rhode Island	19
Missouri	78	Vermont	5
Nebraska	47		260
North Dakota	9	<i>U S Possessions</i>	
Ohio	183	Canal Zone	9
South Dakota	7	Hawaii	10
Wisconsin	64	Philippine Islands	7
	1037	Puerto Rico	13
<i>Southern States</i>			39
Alabama	28	TOTAL UNITED STATES	3583
Arkansas	23	Canada	81
Florida	33	Europe	38
Georgia	57	Asia	25
Louisiana	60	South America	11
Mississippi	14	Mexico	5
North Carolina	67	Australia	4
Oklahoma	46	Central America	3
South Carolina	17	Africa	2
Tennessee	48	West Indies	2
Texas	118		171
	511	TOTAL FOREIGN	171
		GRAND TOTAL CIRCULATION	3754

OBITUARIES

DR JOHN DENNISTON WILSON

Dr John Denniston Wilson (Fellow), Scranton, Pa, died June 20, 1936, of coronary artery disease. He was born in Indiana, Pa, on October 13, 1879, attended the Indiana State Normal School and later graduated from the Jefferson Medical College of Philadelphia in 1905. From 1906 to 1908 he was Demonstrator in Pathology at Jefferson Medical College, from 1905 to 1908, Assistant Pathologist at the Philadelphia General Hospital, in 1910 he went to Scranton and became affiliated with the Scranton State Hospital and continued the association for twenty-five years. He was a Consultant at the Carbondale General Hospital and the Nanticoke State Hospital. He had pursued postgraduate study at Koemigsberg, Berlin, Vienna and at the University of Pennsylvania Graduate School of Medicine. He was a member of the Lackawanna County Medical Society, Pennsylvania State Medical Society, the American Heart Association, the American Medical Association, and had been a Fellow of the American College of Physicians since 1928. He was a volunteer during the Spanish-American War, and served on the Medical Advisory Board during the World War.

Dr Wilson had attained a position of prominence in the medical profession of his City and community. He took an active part in the affairs of his local society and was instrumental in bringing leading medical men to Scranton.

DR ARTHUR BROWN CHASE

Dr Arthur Brown Chase was born in Lynn, Massachusetts, on February 19, 1870. After attending school there he entered Harvard University School of Medicine, where he graduated in 1892. He interned for two years at the Lynn Hospital, and then remained for twelve years in his native city in private practice. He then went first to Atchison, Kansas, and later to Oklahoma City, where he remained the rest of his life. He married Florence Aldous (who survives him) on July 9, 1910.

He was a member of the Men's Dinner Club, a thirty-second degree Mason, a member of the Episcopal church, Alpha Kappa Kappa Medical Fraternity. He was made a Fellow in the College of Physicians in 1920, and was also a member of the Southern Medical Association.

He has been connected with the University of Oklahoma School of Medicine, after coming to Oklahoma City, in varying capacities up until 1926, when he was made a Professor of Clinical Medicine. In 1936 he was made Professor of Medical Ethics.

He took an active part in organized medicine, regularly attending meetings at home and abroad. He was a past president of the Oklahoma County Society and was Councilor of the State Association at the time of his death.

He gave freely of his time and talents in furthering the cause of organized medicine

A chronic heart lesion curtailed his activities, so he perfected himself in Cardiology. He was known well and most favorably in the State, as well as out of it in that particular branch of medicine

For the past two years he had been noticeably failing in health, but kept on with his work until July 8, on leaving his office, he fell and hit his head on a concrete pavement, producing a sub-arachnoid hemorrhage. He improved for a week and a faint hope was held for his recovery, when he began to sink and died July 20

Dr Chase was a genial soul and loved by his confreres. He especially liked to talk to medical students, interns, and those interested in medicine, and wielded a powerful influence for good with those with whom he came in contact. His numerous friends feel a great void since his passing

LEA A. RIELY, M.D., F.A.C.P.,
Governor for Oklahoma

DR. MARTIN J. SYNNOTT

Dr Synnott, the son of the late Mr. and Mrs. Joseph A. Synnott, was born in Great Neck, Long Island, in 1869. His parents moved to Montclair when he was one year old and he resided in that vicinity thereafter. He obtained his preliminary education in the public school of Montclair and graduated from the Montclair High School in 1887. Following this he entered Yale University from which he graduated with a B.A. degree in 1892. Two years later he obtained his M.D. degree from the College of Physicians and Surgeons of New York City.

In 1905 he received an M.A. degree from Yale which was followed by further graduate work abroad in the various clinics of Edinburgh, Berlin and Vienna. He also studied at St. Mary's Hospital, Paddington, London, and at the Harvard Medical School.

Dr Synnott was a prolific writer of medical articles and kept in close touch with everything medical or pertaining to public health in Essex County and was a member of the Montclair Board of Health.

He entered the World War as Captain and was discharged as Major in 1918. At the time of his death he was Colonel in the U.S. Army Medical Reserve Corps.

Dr Synnott was a member of the Essex County and New Jersey State Medical Societies, the American Medical Association, the American Therapeutic Society and the American Proctological Society. He was elected a Fellow of the American College of Physicians in 1923.

At the time of his death he was proctologist at Midtown Hospital, New York City, and Chief, emeritus, of the Medical Staff of St. Vincent's Hospital and had practiced Gastroenterology and Proctology for thirty-six years.

He was a member of the Immaculate Conception Church, Knights of Columbus and the American Legion

Dr Synnott's first wife, the former Miss Jane Agnew of Paterson, died in 1923. He married Miss Eleanor Southworth Hopkins in 1925, who survives him. He is also survived by a son, Paul A. Synnott of Port Chester, N. Y., a daughter, Miss Jane Synnott of Montclair, and a step-son, Ralph Hopkins, and a step-daughter, Miss Natalie Hopkins of Montclair.

Both the medical profession and the College have incurred a great loss in his untimely death.

CLARENCE L. ANDREWS,
Governor for New Jersey

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A COMMON LESION OF THE CERVICAL SPINE RESPONSIBLE FOR SEGMENTAL NEURITIS *

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VON BECHTEREW,¹ Strumpell,² and Marie³ described many years ago some of the neurological problems associated with arthritic changes in the vertebral column. These early investigators observed variable clinical pictures in their cases of spinal arthritis and frequently found that there was no direct relationship between the arthritic change and the intensity of the neurological symptoms. Spastic, atrophic, or hypertonic motor changes and irritative sensory phenomena, or occasionally anesthesia and flaccid paralysis were present in certain of their cases with arthritic changes in the vertebral column.

In 1916 Nathan,⁴ who had observed numerous cases of spinal arthritis with neurological symptoms, induced experimental non-suppurative arthritis in animals in order to study the relationship between the pathological changes and the resulting symptomatology. Evidences were obtained of thickening of the periosteum of the vertebrae, thickening of the connective tissue in the region of the costo-vertebral joints and epidural exudate infiltrating the epidural areolar spaces. It was felt that these changes could lead to irritation and compression of nerve roots, the symptomatology depending upon the degree of nerve root involvement.

Williams and Yglesias⁵ studied the lumbar spine of a large number of cases suffering from sciatica and demonstrated a rupture of the nucleus pulposus with resulting collapse of the intervertebral disc and narrowing of the space between the fifth lumbar vertebra and the sacrum. Schmoil⁶ had previously described these findings in his studies of autopsied material. This condition caused a subluxation of the facets and a constriction of the intervertebral foramina. Subsequent irritation and compression of the fifth lumbar nerve roots produced the painful symptomatology observed in these cases.

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In 1934 Nachlas⁷ described a syndrome of pseudo-angina pectoris originating from demonstrable changes in the cervical spine. Each of the three cases described by him had a definite arthritic involvement of the lower cervical spine associated with thoracic pain. Irritation and compression of the cervical nerve roots secondary to these arthritic changes was felt to be the cause of the referred pain along the medial anterior thoracic and lateral anterior thoracic nerves. These nerves are motor pathways and supply the pectoralis major and minor muscles. Nachlas noticed that acute hyperextension and lateral bending of the neck produced a stab of pain referred to the region beneath the scapula or in the precordium of his patients.

Hanflig⁸ has recently described a group of 30 cases of pain in the shoulder girdle, arm and precordium due to cervical arthritis. He noted certain relatively characteristic clinical features of arthritis of the cervical spine, of which he placed rigidity and pain as the two most outstanding symptoms. He described these cases as frequent and as representing a large group of elderly individuals with symptoms commonly classed as neuritis. A successful method of treatment by traction and manipulation of the neck had been used on his patients.

This paper deals with a critical survey of over 50 patients observed by the authors during the past four years. It is presented because of the presence of a common finding in the cervical spine consisting of a distinct and clear cut narrowing of one or more of the intervertebral spaces.

Most of the patients in this group were over 50 years of age although two patients only 27 years old are included.

Pain in some part of the shoulder girdle, arm, hand, back, precordium or neck was usually the chief complaint though a few cases gave muscular weakness or inability to perform certain normal movements of the upper extremity as the most troublesome symptom. The pain described by patients was quite variable in degree and type. Some complained only of paresthesias while others experienced severe radiating pains. The location and types of pain observed in this group are outlined below.

- 1 Pain in one or both shoulders
- 2 Pain radiating down the arms (usually unilateral)
- 3 Pain on the radial side of the forearm and wrist
- 4 Tingling sensations in the fingers
- 5 Local painful spot between the scapulae
- 6 Pain under one scapula
- 7 Pain low in the neck (posteriorly)
- 8 Pain on turning the neck to one side
- 9 Precordial distress, diagnosed in several cases as aortitis or angina
- 10 Pain exaggerated by walking or riding
- 11 Inability to sleep because of pain in the recumbent posture
- 12 Pain accompanied by limitation of certain types of movement of the upper extremities

Pain was usually unilateral although it had shifted from one upper extremity to the other after months or years in several of the cases. In each of the instances where pain had shifted from its original site to the opposite side there has been a residual weakness of the muscles in the previously involved extremity. There was a simultaneous bilateral involvement in only a few of our cases. Most of the patients were not conscious of pain in the neck and, with two exceptions, did not give this as part of the chief complaint. With two exceptions there was no definite restriction of neck movements on passive or active turning of the head and neck in all possible directions. Whenever a patient complained of exaggeration of pain on walking, immediate, and in one case total, relief of this complication was obtained by having the patient wear soft rubber soles and heels. Pain over one shoulder was the most common of all chief complaints. Most of the patients had been suffering for months or years and had been subjected to various treatments. The story usually included a diagnosis of arthritis in the shoulder and treatment had been directed towards relief of the symptoms in that region. Salicylates had been used in some form by all of these patients. Only passing relief or no relief at all had been obtained from the use of salicylates. Some had been subjected to almost every conceivable form of treatment including ultra-violet light, diathermy, other forms of dry and moist heat, deep roentgen-ray therapy, ointments, liniments, massage and even cautery over the shoulder. Several patients had been treated for elevated blood uric acid because of a "uric acid diathesis." Unfortunately we found that no blood studies had been made on such cases prior to the use of cinchophen and allied substances. Blood studies in our laboratories in these patients failed to reveal an abnormal uric acid level. Obtaining little or no relief, these patients had become "medical drifters" going from one physician to another, even visiting the village cautery expert or some other irregular healer in an attempt to gain aid.

Next to pain the most common chief complaint was weakness in one upper extremity or an inability to perform certain normal movements. In some instances these disturbed movements were undoubtedly secondary to the pain elicited and were associated with some spasticity. In other cases they were the result of actual atrophic changes. Several patients complained of difficulty in writing. One patient, a nurse, found that she could no longer hold her pen properly and that it would slip from between her thumb and index finger when she started to write. In both male and female patients we observed numerous instances of inability to raise the arm in the type of movement involved in brushing or combing the hair. Placing a hat on or removing it from the head was a difficult procedure in some instances. Several women encountered great difficulty in fastening the buttons in the back of their dresses. In one instance a physician had difficulty in writing and in grasping the steering wheel of his automobile. The majority of these patients were unable to elevate the hand above the head in the position of abduction of the arm as in the Fascist salute. With two exceptions there

was no restriction of active or passive neck movements. Furthermore there was no observable limitation of movements of the cervical spine, when compared to normal individuals, on roentgen-ray examination in different positions.

Atrophy of the small muscles of the hand has been present in some instances. The hands of these patients may suggest an amyotrophic lateral sclerosis, syringomyelia or progressive muscular atrophy if both sides are involved. When the atrophy is unilateral the condition is suggestive of an accessory cervical rib—a possibility which can easily be eliminated during the roentgenologic study.

Although the types of spinal changes observed roentgenologically have been variable there has been one consistent finding in all of our cases. This has consisted of a narrowing of one or more of the intervertebral spaces in the cervical spine. If neurological symptoms existed in the patient and directed us towards examinations of the cervical spine this narrowing of one or more interspaces was found present regardless of whether we were dealing in addition with hypertrophic arthritis, infectious arthritis or with a traumatic displacement. Furthermore by a special technic developed by one of the authors (Oppenheimer) it was possible to demonstrate by roentgen examination an accompanying narrowing of the intervertebral foramen at the same levels. (The roentgen technic involved is being described in a separate paper.) This narrowing of the interspaces was present in some cases in which there was no roentgenological evidence of "spicule" or exostosis formation. In numerous instances marked hypertrophic changes, such as marginalipping of the vertebral bodies, were present but the narrowing of the intervertebral spaces also existed. These hypertrophic changes when present always involved the vertebral bodies on either side of a narrowed intervertebral space. One case, a young woman teacher 27 years of age with pain between the scapulae, showed arthritic changes between the fourth and fifth cervical vertebrae suggesting infectious arthritis. Another young woman of the same age showed a narrowing of the interspace between the fifth and sixth cervical vertebrae and a slight anterior displacement of the third and fourth cervical vertebrae.

The following case histories are given in some detail in order to illustrate the findings observed in this group of cases.

CASE HISTORIES

Case 1 V. D., a woman, 76 years of age. Complained of marked pain in the left shoulder with weakness of the right arm. The pains were greatly increased on walking or riding in a car. According to her statement pain began first in the right thumb about 17 years ago. This was followed by a dull pain in the whole right arm with definite limitation of movement so that it became difficult for her to comb her hair or to button her dresses at her back. The pain in the right arm gradually subsided after some years but never completely disappeared. Limitation of movement and residual weakness persisted in spite of this relief from pain. Seven months ago her left arm and shoulder became painful. Pain then increased in both shoulders.

and arms and eventually became so severe on the left side that she was unable to sleep comfortably. She experienced the greatest discomfort when lying on her back and soon learned that relief could be obtained by placing pillows under the head and bending the neck acutely forward. Marked weakness similar to that previously observed in the right arm began to develop in the left upper extremity. Combing the hair became so difficult that she had her hair cut off short to avoid the necessity of raising the arms to the head. The pain in the arms was invariably increased by walking or riding. When walking, the left arm and shoulder annoyed her so greatly that she developed the habit of holding the left hand in the right to protect the arm against undue movement. She had resorted to innumerable forms of treatment such as diathermy, hot compresses over the shoulder, liniments, ointments, massage locally and salicylates internally without relief.

Physical examination revealed no limitation of passive movement in the shoulder joints. She could not internally rotate the left arm and place the hand behind her back without eliciting marked discomfort. Elevation of the arm in abduction was impossible with either the right or left upper extremity. There was no atrophy of the shoulder girdle, arm or hand muscles. Passive and active movements of the neck were not limited and were not painful. There was no rigidity of the neck musculature.

Roentgen findings revealed that the intervertebral spaces between the fifth and sixth and sixth and seventh cervical vertebrae were definitely narrowed. There was a slight increase in bony density seen in the surfaces of these vertebrae. No exostotic formation, no rarefaction and no deformity of the bodies of the cervical vertebrae were observable. The diseased part was shifted slightly backward. Radiography of the entire spine was then made and no changes similar to those seen in the cervical spine were observed in the lower segments. The body of the twelfth dorsal vertebra was deformed, being flattened in its anterior portion. (Close questioning revealed an old fracture resulting from a fall off a ladder 42 years previously.) Roentgen-rays in different positions revealed no limitation of excursion of vertebral bodies in the cervical region during active movements. (Figure 1)

It is of special interest in this case to note that the patient observed relief from pain by bending her head forward. This movement relieved the pressure on the nerves in the region of the intervertebral foramen by temporarily widening the foramen. Because her pains were so aggravated on walking she was advised to replace her leather shoe soles with soft rubber soles and heels. This gave remarkable relief immediately from the discomfort on walking. Ultra short wave and deep roentgen-ray therapy over the cervical vertebrae has brought about marked improvement.

Case 2 A S, nurse, aged 54 years. The chief complaint was pain in both shoulders during the past three months. Her discomfort was most marked in the right shoulder. Certain movements, such as internal rotation of the arm and placing the hand in the middle of the back, caused great discomfort. Fastening a dress with the buttons or hooks in back had become impossible. At times her right shoulder felt quite numb. Three years previously she had noticed weakness in the right hand which was most troublesome when she was holding a pen. The pen would slip from between her thumb and index finger if she attempted to write for any length of time. About a year ago she noticed that the fleshy part of the right hand between the thumb and index finger was becoming sunken and flat. Recently the pain has been variable in intensity, sometimes radiating down the outer aspect of the right arm. On investigating her history closely it was found that 15 years ago she had had a very sudden attack of severe cervical pain a short time after a fall from horseback. At that time she was unable to turn her head to the left because of pain and it was necessary for a physician to administer several morphine injections for relief.

Examination of the shoulder joints revealed negative findings. Passive movements were free and unrestricted. She could not elevate the right hand above her head with the arm in abduction. She was unable to place the right hand in the



FIG 1 *Case 1* Showing narrowing of joint spaces between the fifth and sixth and sixth and seventh cervical vertebrae. Note the absence of lipping.

middle of her back over the sacrum and elevate the hand along the spine. This movement could be made passively although elevation of the hand along the vertebral column was more limited on the right side than it was on the left. The grip of the right hand was much weaker than that of the left. There was marked atrophy of

the soft tissues between the thumb and index finger of the right hand. No atrophy of the shoulder muscles on either side was present and the reflexes of both arms were present and normally active. There was no limitation of motion of the spine in the cervical region. The original diagnosis suggested on hearing her story and noting the atrophy of the small muscles of the right hand was an accessory cervical rib.

Roentgen findings revealed narrowing of the interspaces between the fifth and sixth and sixth and seventh cervical vertebrae. The bodies of the sixth and seventh vertebrae were flattened, their upper and lower surfaces irregular in contour and increased in bony density. There was moderate exostotic formation along the anterior borders of these vertebrae. There was no cervical rib. Roentgen diagnosis was atrophy of intervertebral discs with narrowing of the interspaces and hypertrophic spondylitis in the lower cervical spine (Figure 2).

This patient has obtained great relief from the pains in the shoulder and arm by forcible traction on the head. Relief was noticed following the first two treatments. All other methods of treatment were discontinued.

Case 3 V K, a woman, 27 years of age. The chief complaint was pain in the lower part of the back of the neck between the shoulder blades and over the shoulders (This was one of the two cases giving pain in the neck as the chief complaint). She had experienced recurrent pain in the back, shoulders and lower neck for several years. She felt that her troubles began following a diving accident and later a fall from a horse. There has been no radiation of pain down the arms. She has found it difficult to turn the head to the left when the pain was present.

Physical examination revealed a healthy young woman with no limitation of movement in the shoulder joints on passive or active manipulation. There was a localized tender spot over the second dorsal vertebra and limitation of movements of the cervical spine. Turning the head to the extreme right or left was difficult and painful. Hyperextension of the neck as in lifting the head when the patient was in a prone position was also very painful.

Roentgen findings showed a deviation of the cervical axis due to anterior displacement of the third and fourth cervical vertebrae. No bony pathologic lesion was seen within the bodies of these vertebrae. The intervertebral space between the fifth and sixth cervical vertebrae was narrower than the other intervertebral spaces. There was no demonstrable abnormality in the thoracic spine. The roentgen diagnosis was a definite abnormality in position of the cervical spine probably post traumatic with narrowing of one intervertebral space (Figure 3).

This patient was treated by traction on the head while lying in a supine position. The head was slowly turned from side to side while traction was exerted. Considerable relief was experienced following the first treatment. Physiotherapy in the form of traction and deep massage caudally over the upper thoracic spine while the patient was required to elevate the head and rotate it resulted in complete relief following three treatments.

Case 4 A K Z, a male banker, 53 years of age. The chief complaint was pain on raising the left shoulder, and a localized painful spot on the lower end of the right radius just above the wrist. The pain and limitation of movement in the left shoulder had gradually been increasing for the past several months. Discomfort was most marked during the night and early in the morning. It was difficult for him to raise the left arm when he put on his coat. Massage, heat, diathermy and baths had been used with no relief. He had also been informed that the pain in his shoulder was the result of an increase in the blood uric acid (diagnosed as a case of "uric acid diathesis") but he had obtained no relief from the use of atophan and other remedies. The left arm felt weak and heavy. For the past two weeks he had begun having a painful spot on the lower end of the right radius and felt that the

right hand was not as strong as formerly. His chief concern was a fear that he was developing a paralysis that would invalid him. One physician had frightened him badly by explaining that the pain in the left shoulder was the result of an aortitis.



FIG 2 Case 2 Oblique view showing actual narrowing of one of the intervertebral foramina

Examination revealed a well nourished male who was not acutely ill. There was no limitation of neck movement in any direction. It was impossible for the patient to elevate the left arm above his head. He could not internally rotate this arm and place the left hand behind his back. On relaxation it was possible to move the left

shoulder joint freely by manipulation of the arm. There was no local tenderness over the painful spot over the lower end of the right radius. Careful physical examination did not reveal any evidence of aortitis. Blood pressure was normal and the



FIG 3 Case 3 Showing deviation of the cervical axis due to anterior displacement of the third and fourth cervical vertebrae and narrowing of the interspace between the fifth and sixth cervical vertebrae

cardiac contour was within normal boundaries. He was advised to have a roentgen-ray examination of the cervical spine and for the sake of reassurance to have also a roentgen-ray examination of the chest.

Roentgen findings revealed a classical hypertrophic spondylitis of the lower cervical spine with lipping present on the anterior lips of the fifth and seventh cervical vertebrae. There was also a marked narrowing of the interspace between the fifth and sixth and the seventh cervical and first thoracic vertebrae (Figure 4)



FIG 4 Case 4 Showing hypertrophic spondylitis of the lower cervical spine with lipping of vertebral bodies and narrowing of the intervertebral spaces

The patient was advised to have a series of deep roentgen-ray and short wave treatments over the cervical spine combined with traction treatments. Although the patient was a well educated, intelligent individual he proved to be a skeptic and sought further medical advice. About a week later the patient returned quite worried over

the fact that further study had revealed that his heart was responsible for the pain in the left shoulder while the pain in the right radius was the result of a fracture. The patient was naturally greatly upset. We again advised him that his cardiac findings were normal and that the changes in his cervical spine were quite sufficient, in our



FIG 5 *Case 5* Showing narrowing of the interspace between the fourth and fifth cervical vertebrae with changes suggesting infectious arthritic involvement

opinion, to be responsible for the symptoms in the left shoulder. He was advised that we could find no evidence of a fracture in the right radius and that in all probability the pain complained of in this region was also referred pain secondary to the narrowing of the interspace in the cervical spine. As he was still not fully con-

vinced roentgenograms of both wrists were taken to demonstrate the absence of any bony lesion in either radius. He then consented to undergo neck traction treatment. The local pain in the right wrist disappeared following the first three treatments and there was marked improvement of the symptoms in the left shoulder within a week. Treatment was continued for two weeks and up to the present time (one month) there has been no recurrence of pain in either upper extremity.

Case 5 M. F., a woman teacher, 27 years of age. This patient was first observed by one of us in September 1932 at which time she complained of pain in the right arm and shoulder of nine months' duration. This pain had gradually increased in severity and was variable in its intensity. Sometimes the pain was so severe that it made her cry from discomfort during the night. Movements of the right arm, especially such movements as were involved in combing her hair, were exceedingly uncomfortable. She had also noticed that writing, sewing or knitting was associated with a feeling of weakness and fatigue in the right arm and hand.

Examination revealed no actual involvement of the shoulder joint and movements were quite free in all directions. There was no muscular atrophy of the shoulder or arm. There was limitation of movement of the neck laterally with muscular spasm when extreme lateral movements were attempted. A local pain spot was present under the right scapula.

Roentgen findings revealed that the intervertebral space between the fourth and fifth cervical vertebrae contained a few hazy calcifications. The anterior ligament connecting the bodies of these two vertebrae was calcified and the whole interspace was narrowed. The upper thoracic spine was normal. The changes in the cervical spine had the appearance of those seen in the infectious rheumatic type of arthritis (Figure 5). Search for foci of infection was instituted and the teeth carefully cared for. The patient experienced some relief from autohemoclysis and sterile milk injections intramuscularly. Salicylates had more effect in this case than they did in most of the other cases of our series. Traction on the neck, which was prescribed first, gave in this instance only partial relief.

DISCUSSION

In the five cases presented we have attempted to select histories demonstrating the different types of roentgen findings observed in our group of 50 cases. It will be noted that hypertrophic, post traumatic and rheumatoid changes have been included. Some of the patients showed no actual bone change of either the hypertrophic or rheumatoid type. All of the patients in this group had clear cut narrowing of one or more intervertebral spaces.

If one studies the relationships of the intervertebral foramina through which the nerves pass as they leave the spinal canal in the cervical region, it is quite obvious that narrowing of the interspaces between the vertebrae can and does change the diameter of these foramina. This narrowing can of course be doubly troublesome if there should happen to be exostosis formation around the foramen as well as atrophy of the intervertebral disc. Consideration of the relationships of these foramina also helps to explain why some patients have found it much more comfortable to sleep with the head propped forward since it will be seen that this position tends to widen the foramina while hyperextension increases symptoms because the borders of the foramina shorten the diameter in this position. Any inflammatory changes occurring around the nerves as they pass through these foramina

would also tend to aggravate the situation. Referred pain along the distribution of the fibers involved then takes place.

The middle and lower cervical regions were most commonly involved in our cases. This gives us a clue as to the cause of the frequent shoulder pain. The fourth cervical segment supplies the sensory innervation over the top of the shoulder, and the fifth cervical segment supplies the sensory innervation of the outer surface of the arm between the shoulder and elbow. The deltoid muscle is supplied by nerve fibers derived from the fifth and sixth cervical segments. Shoulder pain and limitation of certain types of shoulder movement should be an indication for study of the cervical spine. This is especially true of pains that are not associated with actual arthritic changes in the shoulder. One of the most common mistakes in regard to these shoulder pains is to regard them as indicative of heart disease.

It was pointed out at the beginning of this paper that most of our patients were over 50 years of age. If there is any indication of precordial distress or if the pain is limited to the left shoulder and arm it is rather natural to check on the state of the heart and large blood vessels. It must be remembered that these elderly individuals usually have aortic shadows more dense than those seen in younger people and that the diagnosis of an aortitis or aortic sclerosis as the cause of the referred pain should be made with caution unless very obvious pathology exists. On the basis of our observations we strongly advise that patients with shoulder pains or precordial distress be subjected to a fluoroscopic examination of the cervical spine as well as roentgen examination of the heart and great blood vessels.

The problem as to the actual etiology of hypertrophic arthritis of the spine is still unsettled. The observations made in our series of cases may help to explain the formation of exostoses seen in this type of arthritis. Since all cases in this group have shown a consistent narrowing of one or more interspaces we are led to believe that this narrowing may be the first change of importance that takes place in many or perhaps all of these cases that later develop hypertrophic spondylitis. The thinning of the intervertebral disc must greatly increase the trauma of the vertebral bodies especially along their margins. This traumatic factor alone could in time be responsible for sufficient irritation along the vertebral margins to produce the formation of exostoses and the lipping so frequently seen in this disease. This is being offered merely as a possible explanation but corresponds to the dog experiments of Compere and Keyes^{9,10}.

We are inclined to agree with Hanflig in regard to his statement that these cases are quite common. If they are kept in mind and actually looked for they will be seen from time to time in every physician's office. They constitute a group that is commonly misdiagnosed repeatedly and that frequently becomes medical "drifters" because of the absence of physical findings in the neck. This can be largely avoided by more careful history taking and roentgenological examination. Furthermore the question of referred pain in relation to changes in the cervical spine should be constantly

kept in mind when dealing with problems involving pain or disturbed movement of the neck, upper extremity and chest. Close questioning of these patients will frequently reveal severe trauma of the spine at some previous time, often many years earlier.

Some of these patients obtain marked relief by means of neck traction. Hanflig's technic of traction using a Sayres sling suspension with block and tackle arrangement is perhaps the most simple method. Manual traction and manipulation will give satisfactory results in some cases although it is exceedingly strenuous exercise for the manipulator. Some cases are relieved greatly by the use of ultra short wave therapy directly over the cervical spine. The use of soft rubber soles and heels is advisable for all patients suffering from pathologic lesions in the cervical spine.

Further discussion of the roentgen findings observed in this group of cases is being presented in a subsequent communication.

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ACUTE PNEUMONITIS

By WILLIAM H. ALLEN, M.D., F.A.C.P., *Fort Sam Houston, Texas*

It is doubtful if there is anything in medicine presenting greater difficulty in classification than the so-called respiratory diseases. In every outbreak the problem arises when to cease the use of such terms as nasopharyngitis and acute bronchitis in order to adopt the equally indefinite one of influenza. One is confronted with the same difficulty in placing the pneumonias, though some progress is being made toward adoption of an etiological classification. It is with no wish to add to the prevailing confusion that we have found it useful to classify as acute pneumonitis a group of cases characterized by signs of respiratory infection, benign course, few physical signs, and roentgenographic evidence of a localized pulmonary involvement.

The dictionary gives pneumonitis as a synonym of broncho-pneumonia. Pathologically, this may be true but clinically and roentgenologically it represents a definite group, possibly a sub-group of the so-called broncho-pneumonias.

During the year 1935, there were admitted to the Medical Service of the Station Hospital, Fort Sam Houston, 2081 cases of respiratory disease. Of these, 53 were classed as primary lobar pneumonia, 16 as primary broncho-pneumonia, and 68 as acute pneumonitis. From the last I have selected 50 cases for analysis. It is doubtful whether this represents the true incidence of the condition as only in the more severe cases of respiratory infection were chest films made. As the diagnosis must be made almost solely by this means there appears to be no doubt that pneumonitis is generally overlooked. This is borne out by the paucity of reference to it in the literature.

Etiology This is uncertain but as all these cases occurred in the general group of acute respiratory infections it may be assumed that a filtrable virus with a secondary invasion by the ordinary bronchial tract organisms was the causative factor. While pneumococcus typing is carried out in all primary pneumonias, no effort was made to do so in the majority of these cases here reported. In a few, group IV pneumococci were isolated, in others, no pneumococci were found.

Due to the regulations governing admissions to our service, the great majority of the patients reported were young, adult males, but one female being included in the present analysis. The minimum age was 9 and the maximum 51 with an average of 25.5. We are unable to judge of the true age and sex incidence of this condition.

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Pathology As there were no deaths in this series or in others that I have seen no definite knowledge of the pathology exists The lung lesion may be visualized as an inflammatory and exudative process extending from the bronchioles into the alveoli over a localized portion of a lobe or lobes The involvement was predominantly of one or both lower lobes in 92 per cent



FIG 1 Pneumonitis extending from the right hilum

TABLE I
Lobes Involved

	Cases	Per cent
Right lower	18	36 0
Both lower	15	30 0
Left lower	11	22 0
Right all	2	4 0
Right middle	1	2 0
Right upper	1	2 0
Left upper	1	2 0
Both upper	1	2 0
	<hr/> 50	<hr/> 100 0

of our cases with the greater incidence on the right side. Taking the lungs as a whole, the right was involved in 44, the left in 24, and both in 32 per cent.

Symptoms On admission the patients complained of the usual symptoms of acute respiratory infection—cough, fever, malaise, and “cold in the head.” There was a noticeable absence of the ordinary symptoms of pneumococcus pneumonia, such as initial chill, sharp pain, and rusty sputum.



FIG 2 Pneumonitis of left lower lobe

When there was complaint of pain in the chest it was described as a dull aching or sense of fulness. In no case was there the stabbing pain of pleural involvement. This may be explained by the fact that the involvement was almost invariably central.

The maximum temperature was usually recorded within a day or two of the onset. Defervescence was commonly rapid though in a number of cases a low grade, irregular fever persisted for many days. The maximum temperature is shown in table 3.

TABLE II
Symptoms on Admission

	Cases	Per cent
Cough	43	86 0
Fever	35	70 0
Malaise	27	54 0
"Cold"	27	54 0
Pain or soreness in chest	15	30 0
Sore throat	14	28 0
Headache	14	28 0
Weakness	4	8 0
Chill	4	8 0
Nausea or vomiting	3	6 0
Bloody or blood-tinged sputum	2	4 0
Abdominal pain	2	4 0
Stiff neck	1	2 0
Vertigo	1	2 0
Night sweats	1	2 0

TABLE III
Maximum Temperature

	Cases	Per cent
99'-100'	4	8 0
100'-101'	9	18 0
101'-102'	10	20 0
102'-103'	15	30 0
103'-104'	7	14 0
104'-105'	5	10 0
	<hr/> 50	<hr/> 100 0

Physical Signs These were conspicuous by their absence. As shown in table 4, 36 (72 per cent) had fine or medium moist râles over the involved area, while 10 (20 per cent) had no demonstrable signs. In a large proportion no râles were found at the time of admission, these appearing from one to three days later. Impaired resonance was found in but 3 (6 per cent) and broncho-vesicular breathing in but 1 (2 per cent).

TABLE IV
Physical Signs

	Cases	Per cent
Fine or medium râles	36	72 0
Coarse râles	3	6 0
Impaired resonance	3	6 0
Broncho-vesicular breathing	1	2 0
Friction rub	1	2 0
No signs	10	20 0

The maximum leukocyte count was below 14,000 in 78 per cent of the cases, and in 54 per cent it was 10,000 or less.

TABLE V
Maximum Leukocyte Count

	Cases	Per cent
5000-7000	12	24 0
8000-10000	15	30 0
11000-13000	12	24 0
14000-16000	7	14 0
17000-20000	3	6 0
Above 20000	1	2 0
	<hr/> 50	<hr/> 100 0

Roentgenological Signs Major Bowen of the Army Medical Corps, to whom I am indebted for the roentgenologic studies in these cases, has recently described the findings in influenzal pneumonitis as follows

Influenzal pneumonitis involves only a portion of a lobe, usually basal, though it has been seen in the upper lobes and involving more than one lobe without increase in symptoms. It extends outward from the hilus well into the parenchyma, occasionally reaching the periphery. The roentgen appearance is that of a confluent mottled fan or rounded area, usually of homogenous moderate density in the central portion, with the borders fading into the normal lung. It has the appearance of an exudative alveolar infiltration and is usually more localized and of more even density than the bronchopneumonias of childhood or than those which complicate adult diseases. The usual picture of broncho-pneumonia is a scattered mottling not confined to one lobe or sharply localized.¹

In the present series, 44 per cent showed a single area of pneumonitis while 36 per cent had more scattered infiltration. Eighteen per cent had two areas of increased density, usually involving both lower lobes.

TABLE VI
Roentgenologic Signs

	Cases	Per cent
Single area of pneumonitis	22	44.0
Two areas of pneumonitis	9	18.0
Scattered infiltration	18	36.0
No definite signs	1	2.0
	<hr/> 50	<hr/> 100.0

Complications These were rare. Three cases (6 per cent) developed acute maxillary sinusitis and one each, acute otitis media and urticaria. One case had a peritonsillar abscess with subsequent necrosis of the cervical lymph nodes, requiring operative intervention.

Prognosis There were no deaths in this series. The maximum period of hospitalization was 91 days for the case with peritonsillar abscess and necrosis of the cervical glands, the minimum was nine days, and the average 28 days. This average is in excess of what might be expected in a civil hospital due to the fact that a soldier is not discharged until he is able to return to full duty but it serves to indicate what may be considered the length of convalescence. In the majority of cases hospitalization was prolonged by weakness and the persistence of cough and râles after all other symptoms and signs had subsided.

A better idea of the duration of the disease may be gained from the days of fever as shown in table 7.

TABLE VII
Duration of Fever

Days	Cases	Per cent
1-2	4	8.0
3-5	15	30.0
6-8	12	24.0
9-11	7	14.0
12-15	4	8.0
16-20	2	4.0
Over 20	6	12.0
	<hr/> 50	<hr/> 100.0

Treatment This has been purely symptomatic. Emphasis has been placed on adequate nursing, free use of fluids, and a relatively high carbohydrate intake. Codeine has been used freely for the control of cough.

SUMMARY

1. Acute pneumonitis is used as the designation for a form of respiratory infection characterized by a benign course, few physical signs, and roentgenologic evidence of a localized inflammatory process in the lung.

2. In the absence of deaths the pathology is unknown but it is assumed to be an extension of an inflammatory process from the bronchioles to the alveoli with exudation.

3. The symptoms are those of a moderate to severe respiratory infection.

4. The diagnosis must be made by roentgenography.

REFERENCE

1. BOWEN, A. Acute influenzal pneumonitis, *Am. Jr. Roent. and Radium Therap.*, 1935, **xxiv**, 168-174.

DIVERTICULA OF THE STOMACH

By LAY MARTIN, M D , F A C P , *Baltimore, Maryland*

DIVERTICULA of the stomach are rarities. The average physician has had no experience with this abnormality, and this lack of experience is not limited to the clinical side of medicine, it is also found among the pathologists.

My interest in the subject was awakened by discovering a diverticulum of the stomach in a patient—a patient who wanted to know all about the condition. What should be the treatment—medical, surgical or none? What were the symptoms caused by the abnormality? Did it increase or decrease in size? What was the danger of perforation? How often should a re-examination be made? How often did it occur? What was the chance of malignant degeneration? As a result a study was made of the condition.

An exhaustive search through the archives of the History Department of the Johns Hopkins Hospital was unfruitful in revealing a single case diagnosed ante mortem. Not one was reported after laparotomy. Apparently none was reported by the roentgenologic department. The search was continued through the records of the pathology department and five cases were found. These and one living case are reported below.

CASE REPORTS

Case 1 A physician, aged 40 years, consulted me complaining of indigestion, bloating, distention and at times a gnawing sensation which was partially relieved by food. He was concerned about himself to the point of believing that he had a duodenal ulcer. Certain factors, to him of serious import, had come into his life and made him quite tense. His story was typically one of anxiety neurosis. On physical examination nothing remarkable was noted.

Fluoroscopic examination of his stomach showed an unusual condition. Barium flowed freely through the esophagus and the cardiac orifice. The stomach was in good position, the rugae well defined and regular, and the tonicity normal. To the mesial side of the lesser curvature, in the upper fundo-cardiac portion, was a spherical mass, which was mobile, not tender, clearly defined, of smooth regular outline. This was connected to the stomach by a narrow pedicle. Films made later by Dr. J. W. Pierson, convincingly demonstrated its patency and that it connected the barium filled sphere with the stomach. Hours after the stomach was freed of barium, the diverticulum remained visible. The patient finally solved his personal problems and the gastric symptoms abated. The diverticulum is still as noted above.

Since 1920, five cases of diverticulum of the stomach have been noted in the department of pathology of the Johns Hopkins Hospital. They are given seriatim below. In none of these cases does the clinical history give

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any suggestion of the presence of the diverticulum and such symptoms as were manifest were located in other systems than the gastrointestinal

Case 2 A 39-year-old negro female

Anatomical diagnosis History of sudden convulsive death at operation under procaine anesthesia Operative wound in left thorax cardiac hypertrophy, ascites,



FIG 1 Showing diverticulum of the stomach soon after ingestion of barium sulphate

bilateral hydrothorax, edema of back, chronic passive congestion of lungs, liver and kidneys Diverticulum of stomach Mitral insufficiency

Macroscopic description The stomach is normal in size and contains a small

amount of semifluid food. The mucosa shows postmortem digestion. At the dome of the cardia, there is a small diverticulum about 3 cm across and bulging out about 2 cm. The musculature over this area is greatly thinned out and leaves practically nothing but the mucosa and serosa.

Microscopic description. All muscular coats except that of the mucosa disappear over a small area.



FIG 2 Showing diverticulum of stomach six hours after ingestion of barium sulphate

Case 3. A 59-year-old white male

Anatomical diagnosis. Acute and chronic verrucose endocarditis of aortic and mitral valves. Aortic stenosis and insufficiency, slight scarring of myocardium,

cardiac hypertrophy, chronic passive congestion of lungs and viscera, clubbing of fingers, edema of ankles, mural thrombosis pulmonary emboli, infarcts, and edema. Generalized arteriosclerosis, old scars in kidneys, prostatic hypertrophy, slight hypertrophy of bladder muscle. Dental caries. Diverticulum of stomach. Papillary cystadenoma of kidney. Thrombi in prostatic plexus.

Macroscopic description Near the cardiac orifice the stomach wall is thinned out over an area of about 2 cm in diameter so that a little pouch is formed.

Microscopic description Sections of the stomach taken through the pouch show normal serosa and mucous membrane. The muscular layer is scant.

Case 4 A 60-year-old white male.

Anatomical diagnosis Hypophyseal tumor pressing on optic chiasm with atrophy of right optic tract and nerve. Calcified area on surface of right upper lobe with fibrous pleural adhesions. Caseous tuberculous lymph nodes along trachea and hilum of right lung. Disseminated tubercles in liver, lungs, spleen, kidneys. Obesity. Diverticula in pylorus.

Macroscopic description Just proximal to the pyloric valve there are two diverticula measuring 1 cm in diameter and 1 cm deep, over which the mucosa appears to be intact. Dr. MacCallum: "At the pylorus there is a sacculation with complete lining of mucosa."

Microscopic description The walls of the one diverticulum seen are normal.

Case 5 A 16-year-old negro female.

Anatomical diagnosis Acute necrosis of liver, small liver, jaundice, hemorrhages into endocardium, puerperal uterus, diverticulum in pyloric position of stomach, accessory pancreas. Fresh ulcers in duodenum, diffuse enlargement of thyroid. Calcified vessels in corpus striatum.

Macroscopic description Stomach—about 1 cm from the pylorus there is a small diverticulum in the stomach wall with an opening measuring 5 mm in diameter. It is about 1 cm deep and there seems to be a palpable little tumor at the end of the diverticulum. The lining of the little cavity seems to be normal pale mucosa. There is also a duodenal ulcer.

Microscopic description Stomach. There are two sections which show the stomach. The opening of the small diverticulum is missed. The section one was cut further to show it if possible. However, one shows the space in the wall of the stomach and at the base the little nodule which turns out to be for the greater part made up of gland tissue. There are a few areas of pancreatic tissue.

Case 6 A 28-year-old negro female.

Anatomical diagnosis Encapsulated caseous tubercles in lungs, hyaline and caseous tubercles in tracheal lymph nodes. Disseminated tubercles in spleen, liver, kidneys, intestines and lung. Tuberculous meningitis. Infarcts in spleen, purulent tonsillitis, lobular pneumonia. Cyst in left ovary with hemorrhage. Scarring of pancreas. Syphilis (positive Wassermann). Diverticula of stomach.

Macroscopic description The fundus of the stomach is thinned out, and on the ventral surface of the greater curvature, near the cardiac end, four shallow excavations are seen. Peculiar punctate excavations measuring less than a millimeter, are generously scattered in the mucosa near the cardiac end of the greater curvature, more posterior than the larger ulcers. There is a diverticulum lined with normal stomach mucosa near the pyloric end of the fundus.

Microscopic description The mucosa, muscularis, muscular layer and serosa are intact.

DISCUSSION

The subject about to be discussed offers one of the best examples of that common fault of the medical historian, i.e. the acceptance of previous au-

thors' interpretations of the writings of others. The writers who have made any attempt to outline the history of our knowledge of gastric diverticula all refer to Helmont as being the first to see and report the finding. Voigtel is the authority generally cited for first mentioning Helmont. Those who do not mention Voigtel assert that Helmont in 1804 reported the first case.

To explain the continued reiteration of this inaccuracy, we may best start with the report by M. Fournier³ in 1774. He performed an autopsy on a former patient, whose clinical course had been completely mystifying to him. His description of what he observed on section is of no immediate interest to us until he says that the stomach was filled with numerous foreign bodies such as pieces of iron, wood, etc., and he writes "La forme de l'estomac était un quarre long. On y distinguait aisement quatre faces chacune de quatre pouces de largeur. L'ayant ouvert nous y trouvâmes toutes les pièces détaillées ci-après dans le rapport et tellement arrangées que l'on aurait dit qu'une main adroite les eut placées chacune de façon qu'elles eussent occupées le moins de place possibles." At no point in his article is there any reference to a sac or a diverticulum. In 1804 Voigtel⁴ referred to Fournier's patient, and commented upon the numerous articles swallowed by him. In describing the pathological findings (on page 512) he says "Im Schlunde fand man ein grosses Stuck Holz im Magen aber, innerhalb einen besondern Sack." Surely a misrepresentation of the facts as reported by Fournier.

Another factor which has apparently helped confuse the unwary was Voigtel's⁴ description of a duodenal diverticulum on page 504, under the general subject of *Hydrops Ventriculi*. He writes "In der mitte des Pfortners hing ein mit Wasser gefullten Sack, der eines Fingers lang und einen Zoll dick war, und sich in der Zwolfingerdarm erstreckte." Citing previous references to the subject he refers to page 154 of Moebius'² book, which was published in 1661. Here the author may be quoted "*Hydrops Ventriculi* menit Lazari Riverus in observat communie p. 364 in quo tantus tumor ejus ut ex aperto nonaginta librae aquae effluerent."

It so happens that on page 137 of this same volume of Moebius there is a reference to Helmont "*sacculum ventriculi annatum et lapidibus repletum conspexit Helmont*." Not only does Voigtel not refer to Helmont but his reference to Fournier is incorrect, besides that the diverticulum he himself observed and described was connected with the duodenum.

Another mistake which has been carried on down in the literature is in regard to a gastric diverticulum alleged to have been described by Vasquez⁵ in 1859. A soldier died some time after being badly jarred. On section there was revealed "existencia sobre su parte superior y lado derecho de enorme saco, ciego, al parecer, mas en comunicacion con el esófago por pequenos aquejeros que a modo de regadera daban paso a las líquidas bebidas de que estaba llena su cavidad, y cuyas paredes de mas de un pulgada de grosor ostentaban en su superficie esterna diversas másticos desde el violado

TABLE I

Reference	Author	Age	Sex	Position	Walls of Sac	Observation	Year Reported	Symptoms	Remarks
1	Baillie			not stated	thinned	autopsy	1793	not stated	coins found in pouch
11	Thorel			cardiac	thin muscle serosa	autopsy	1895	not stated	
12	Kleine	45	Male	lesser curvature pyloric	mucosa and thick muscle	operation	1895	not stated	
				loric	mucosa—no mucosa	autopsy	1895	not stated	
				lesser curvature pyloric	thin muscle mucosa and serosa	autopsy	1895	not stated	
13	Kolaczek	45	Female	lesser curvature mid portion	intact	operation	1895	pseudo ulcerous	cured
14	Grassberger	73	Male	posterior wall near pylorus	muscle thin mucosa and serosa intact	autopsy	1897	pseudo ulcerous	
15	Schulten	25	Female	lesser curvature	intact	autopsy	1897	not stated	
16	Ferguson	34	Female	near cardiac orifice	mucosa and serosa	autopsy	1898	not stated	
17	Zahn	53	Male	near cardiac orifice	muscle thin mucosa and serosa intact	autopsy	1899	not stated	
18	Hamilton	59	Male	near cardiac orifice	not stated	autopsy	1901	not stated	
20	Hirsch	46	Male	near cardiac orifice	mucosa and serosa intact	autopsy	1903	not stated	
22	Küss	61	Male	greater curvature pyloric	thin muscle mucosa intact	autopsy	1905	not stated	
27	Jones	33	Male	anterior wall near pylorus	mucosa and serosa only	operation	1909	yes	cured
29	Bromann	Embryo	Female	not stated	intact	autopsy	1910		museum specimen
28	Keith	70	Female	near cardiac orifice	muscle thin mucosa and serosa intact	autopsy	1910		museum specimen
30	Handtmann	adult	Male	near cardiac orifice	serosa intact	autopsy	1910	none	
33	Boreszky	35	Male	near cardiac orifice	mucosa and serosa only	autopsy	1912		
				greater curvature near pylorus	walls intact and filled with blood	autopsy	1911	pseudo ulcerous	cured
35	Brown	53	Male	lesser curvature near pylorus	intact	operation	1914	pseudo ulcerous	cured
36	Secher	32	Male	lesser curvature near pylorus	intact	operation	1916	yes	cured
40	Mellon et al	29	Female	lesser curvature near pylorus	intact	operation	1917	not stated	
41	Oberling	31	Male	greater curvature mid portion	muscle thin mucosa and serosa intact	autopsy	1921	yes	cured
42	Alerlund	54	Male	lesser curvature pyloric	walls intact	operation	1923	yes	died
				greater curvature mid portion	mucosa and serosa only	operation	1923		also duodenal ulcer
43	Rothbart	29	Female	near cardiac orifice		autopsy	1923		also diverticulum of duodenum
		33	Female	near cardiac orifice		autopsy	1923		
		40	Female	near cardiac orifice		autopsy	1923		
		42	Female	near cardiac orifice		autopsy	1923		
		63	Female	near cardiac orifice		autopsy	1923		
		38	Female	lesser curvature mid portion		autopsy	1923		
44	Tupper	43	Male	lesser curvature near pylorus	muscle thin mucosa and serosa intact	operation	1923	present	cured

TABLE I--Continued

Reference	Author	Age	Sex	Position	Walls of Sac	Observation	Year Reported	Symptoms	Remarks
45	Ravenel	65	Female	near cardiac orifice two sacs		x-ray	1923	yes	
16	Coleschi		Male	greater curvature mid portion		x-ray	1923	pain	
18	Stolz and Hickel	48	Female	greater curvature pyloric	intact	x-ray and operation	1923	present	cured
50	Fleischner	62	Male	near cardiac orifice	mucosa and serosa only	autopsy	1924	complication	abdominal cancer
		72	Female	near cardiac orifice	muscle thin, mucosa and serosa intact	autopsy	1924	complication	abdominal cancer
51	Emery	adult	Female	near cardiac orifice		x-ray	1924	questionable	
52	Perusia	18 adult	Male	near cardiac orifice		x-ray	1924	questionable	
			Male	lesser curvature mid portion		x-ray	1924	present	
55	Delherm et al		Female	lesser curvature mid portion	no note	x-ray and operation	1925	present	cured
56	Southerland	51	Male	greater curvature and pylorus two pouches	not stated	x-ray and operation	1925	bleeding	cured
57	Weiss	49	Male	lesser curvature near pylorus	intact	x-ray and operation	1925	pseudo ulcerous	cured
58	Gray	32	Male	near cardiac orifice		x-ray	1925	none	
54	Hurst and Briggs	35	Female	near cardiac orifice		x-ray	1925	yes	postural drainage
		38	Female	near cardiac orifice		x-ray	1925	yes	postural drainage
60	Bordoni	39	Female	near cardiac orifice		x-ray	1926	yes	questionable
61	Thomson	45	Male	near cardiac opening	muscles thin, mucosa thin	x-ray and operation	1926	yes	
62	Brundt	64	Female	near cardiac orifice	intact	autopsy	1926	no	not found at operation
63	Lawson	50	Female	near cardiac orifice		x-ray and operation	1926	no	
64	Jones	42	Male	lesser curvature mid portion		x-ray	1926	yes	
65	Pearlstein	43	Female	near cardiac orifice		x-ray	1926	yes	
68	Bernstein	34	Female	near cardiac orifice		x-ray	1928	none	
69	Kalbfleisch	39	Female	near cardiac orifice		x-ray	1928	none	
70	Goodwin	33	Female	near cardiac orifice		x-ray	1928	yes	
71	Pemberton	Embryo	Female	near cardiac orifice	intact	autopsy	1928		
72	Pansdorf	48	Female	lesser curvature near pylorus	intact	x-ray and operation	1929	x-ray and	
73	Shelton	Infant	Female	not stated	intact	operation	1929	yes	cured
75	Liljedahl	25	Female	near cardiac orifice		x-ray	1929	none	
76	Allan	43	Female	near cardiac orifice	muscle thin, mucosa intact	autopsy	1930	none	
77	Geyman	63	Male	near cardiac orifice		x-ray	1930	yes	
78	Santoro	34	Female	near cardiac orifice		x-ray	1930	yes	
79	Ottomello	18	Female	near cardiac orifice		x-ray	1930	questionable	
		65	Female	near cardiac orifice		x-ray	1930	questionable	
80	Beutel and Mailler	12	Male	near cardiac orifice		x-ray	1930	questionable	
		69	Male	lesser curvature mid portion		x-ray and gastroscop	1930	yes	
81	Anziolotti	59	Female	greater curvature mid portion		x-ray	1930	yes	

TABLE I—Continued

Reference	Author	Age	Sex	Position	Walls of Sac	Observation	Year Reported	Symptoms	Remarks
82	Lenarduzzi	48	Female	greater curvature mid portion	intact	x ray and operation	1931	pain	not found at operation
		54	Female	lesser curvature mid portion		x ray	1931	questionable	2 small diverticula
85	Laurell	16	Female	near cardiac orifice		x-ray	1931	questionable	also diverticulum of colon
		18	Female	greater curvature upper portion		x ray	1931	none	
83	Gile	7	Female	lesser curvature near pylorus		x ray and operation	1931	yes	cured
84	Pendergrass	49	Female	near cardiac orifice		x ray	1931	not started	
87	Bell and Golden	37	Female	near cardiac orifice		x ray	1932	questionable	not found at operation
		30	Female	near cardiac orifice		x ray	1932	yes	associated duodenal ulcer
		45	Male	lesser curvature mid portion		x ray	1932	questionable	
88	Barsony and Koppenstein	65	Male	lesser curvature mid portion		x ray	1932	questionable	associated duodenal ulcer
		54	Male	near cardiac orifice		x ray	1932	no	
		20	Male	near cardiac orifice		x ray	1932	yes	
		63	Male	near cardiac orifice		x ray	1932	yes	helped by atropine
		12	Female	near cardiac orifice		x ray	1932	no	
89	Gutzeit and Kullmann	50	Male	near cardiac orifice		x ray	1932	no	
		56	Male	near cardiac orifice		x ray and gastroscop	1933	questionable	
		29	Male	near cardiac orifice		x ray and gastroscop	1933	no	
90	Bonnet	44	Male	near cardiac orifice	muscle thin mucosa and serosa intact	x ray and operation	1934	bleeding	cured
91	Rivers et al	36	Male	near cardiac orifice	all coats thinned	x ray and operation	1935	present	cured ulcer at pylorus
		28	Female	near cardiac orifice	all coats thinned	x ray and operation	1935	present	no note
		43	Male	greater curvature mid portion	all coats thinned	x ray and operation	1935	present	no note
		30	Female	pyloric	all coats thinned	operation	1935	present	no note
		26	Female	pyloric	all coats thinned	operation	1935	present	cured
		51	Male	pyloric	all coats thinned	operation	1935	present	blood in diverticulum
		49	Male	pyloric	all coats thinned	operation	1935	questionable	ulcer also present
		59	Female	pyloric	all coats thinned	operation	1935	present	cured
		56	Female	cardiac	all coats thinned	autopsy	1935	no note	not cured also had duodenal ulcer
		49	Male	cardiac	all coats thinned	autopsy	1935	no note	
		44	Female	cardiac	all coats thinned	autopsy	1935	no note	
		55	Female	cardiac	all coats thinned	autopsy	1935	no note	
		24	Female	cardiac	all coats thinned	x ray	1935	present	
		44	Male	lesser curvature mid portion		x ray	1935	none	
92	Freiliche et al Martin	39	Female	cardiac	mucosa and serosa only	autopsy	1935	no note	
		59	Male	cardiac	intact muscle thin	autopsy	1935	none	
		60	Male	lesser curvature	intact	autopsy	1935	none	
		28	Female	lesser curvature	intact	autopsy	1935	none	

al claro, propio de las membranas " In this instance there was a traumatic diverticulum of the esophagus, not of the stomach

In spite of the rarity of the abnormality there is quite an amount of literature on the subject, and to avoid the possible continuation of the errors noted above the information presented below has been taken from the original reports. The compiled data on the 103 uncomplicated pulsion diverticula are presented in table 1, and the cases are arranged in their order of publication. Besides this number, the other 22 more or less complicated cases are reported in their turn.

Reports are available from many countries. The earliest authentic case I have found is that of Thomas Baillie,¹ who writes "A part of the stomach is occasionally formed into a pouch by mechanical means, although very rarely. I have seen one instance of a pouch being so formed, in which five halfpence had been lodged. The coats of the stomach were thinner at that part, but were not inflamed or ulcerated. The halfpence had remained there for some considerable time, forming a pouch by their pressure, but had not irritated the stomach in such a manner as to produce inflammation or ulceration." His report has been followed by others, at first, as one might suspect, mainly from Germany. These early cases were noted at autopsy and, although many were reported in full and with suggestions as to etiology and reasons for their position, they were incidental findings. They have been found at all ages. Broman²⁹ and Pernkopf⁷¹ each found one in an embryo and Sinclair⁷³ reported a four months old child who was operated upon for the same condition. The majority of these cases were first observed when the patients were in their thirties, forties and fifties. It has been the habit of most observers to state that the abnormality was most commonly seen in women. Of the 103 cases reported, 54 occurred in women.

DESCRIPTION OF THE ABNORMALITY

There are two general types of diverticula of the stomach.

1 *Pulsion*. This includes the congenital group and also the cases which result from such congenital malformations as a gastric muscle hiatus, a localized absence of gastric muscle, or simply a local weak area of gastric muscle. In the latter sub-division, a sufficient increase of intragastric pressure might distend the weak spot until a pouch or diverticulum was formed.

2 *Traction*. This includes such pouchings, folds, protrusions, niches, etc., as are brought about by disease process (infections, neoplasm) in the gastric wall, or by any process without the gastric wall which will cause it to protrude in any of the conditions noted above.

The diverticula reported in this paper were all of the pulsion type.

POSITION

The most common location for the pulsion type of diverticulum is near the cardiac opening of the stomach. Most anatomists state that in this region the stomach musculature is poorly developed.

TABLE II
Tabulation of Some of the Characteristics of 103 Uncomplicated Pulsion Diverticula of the Stomach

	Mucosa Thinned Muscles		Intact	No Serosa Note only	Cardiac		Lesser Curvature Mid Portion		Greater Curvature Mid Portion		Miscel	Male	Female	Not Stated	Pres- ent	None	Question- able	No Note
Condition of Wall of Diver- ticulum	16	23	6	8														
Position of Diverticulum					63	11	14	5	4	6								
Sex of Patient												43	54	6				
Symptoms															50	16	16	21

From table 2 it is evident that 61 per cent of the diverticula of the stomach are situated within the radius of a few centimeters of the cardia. The other 39 per cent are distributed most frequently along the lesser curvature. They have also been found to occur along the greater curvature and on the anterior and posterior surfaces of the fundus of the stomach. In the living case reported in this paper, and in which the diagnosis was made by roentgen-ray, the diverticulum was situated on the lesser curvature some distance below the cardiac orifice.

HISTOLOGY OF THE WALLS OF THE DIVERTICULA

Diverticula of the stomach may be classified under three headings in respect to the construction of their walls

- 1 Those consisting of one or more layers of gastric tissue,
- 2 Those consisting of gastric tissue plus pancreatic cells,
- 3 Those consisting of tumor cells plus more or less gastric tissue

1 *Various Gastric Layers* In far the greater number of diverticula the stomach walls contain only gastric tissue. From case to case there may be a wide range of difference in the construction of the individual wall, it may consist of anything from gastric mucosa with a covering of serosa to a wall which includes normal muscular and mucosal layers. In table 2 the construction of the wall has been tabulated as intact, muscle thinned with mucosa and serosa present, and mucosa and serosa only. Of the 56 cases in which the diverticulum was examined and described 16 had intact walls, 23 had thinned muscular layers, and six had walls which consisted of mucosa and serosa alone. The other eight were not described.

No case has been included in which the serosa had been distorted to the extent that the diverticulum might be of the traction type. The two diverticula found in embryos were found to be lined with normal mucosa and to have a musculature like that of the rest of the stomach. This was also true in the case of the infant of four months upon whom Sinclair operated. In two of the cases in my series there was a complete absence of musculature over part of the diverticulum. This was demonstrable macro- and microscopically.

A number of investigators have endeavored to further define the characteristics of the two sub-groups (congenital and acquired) of the simple pulsion type. They would classify as congenital those which contain all the layers of the gastric wall. Those which contained thinned musculature, they would classify as acquired. Several of them believe that those whose walls consist of mucosa and serosa only should be called herniations.

It is noteworthy that although there is a great variation in the thickness of the gastric musculature, the mucosa has been found, with one or two exceptions, to be similar to that noted over the remainder of the stomach.

2 *Pancreatic Inclusion* One case of this type is presented in my series

and 14[†] others have been culled from the literature. In only one instance was such a diverticulum found near the cardia, in this patient⁷ there were two diverticula, one as noted and the other near the pylorus. In the other patients the pouch was near the pylorus and (except in three instances) on the lesser curvature. The wall of these diverticula always consisted of the normal gastric layers and the island of pancreatic tissue was usually found at the peak. There seems little doubt that these represent congenital abnormalities. Broman²⁹ feels that they are simply the dilated excretory ducts of hypertrophied pancreatic islands whose acini have not been able to develop normally.

The only two cases which were found at operation were reported in a general article by Moynihan⁶⁷. The finding was accidental, for he was operating for duodenal ulcers. All the others were noted at autopsy. My case is the only one reported in recent years.

3 *Tumors Benign or Malignant* Adenomyoma^{39, 91, 49, 71} have been found in the walls of gastric diverticula on four occasions, carcinoma^{40, 31, 38} thrice and fibrosarcoma once⁹¹.

SIZE AND SHAPE OF DIVERTICULA

As might well be suspected, the diverticula are of various shapes and sizes. The openings may be small and lead through a narrow pedicle into a considerably enlarged sac. Again the diameter of the opening may be the largest dimension, so that the diverticulum assumes a pouch-like appearance. If the sacs do not retain barium, the diverticula will, of course, be undiagnosed roentgenologically, and they may well be missed at operation. The diameters of the sacs of the original cases herein reported vary from 1 by 2 cm. to 5 by 6 cm. This corresponds to the variations of most of the reported cases, although some of them are larger.

The largest was measured by Stolz and Hickel⁴⁸ as 8 by 10 by 20 centimeters. It was removed at operation. Kleime¹² also reported an operative case with a diverticulum the size of his fist. In both, the walls were reported as normal and the pedicle was inserted in the prepyloric region.

Two groups of investigators^{80, 84} cite instances in which small openings of gastric diverticula were seen via the gastroscope.

ROENTGENOLOGIC DIAGNOSIS

Since the use of roentgen-rays for diagnosis of gastric abnormalities, there has been a marked increase in the number of reported cases of gastric diverticula. It is in the past 15 years that the majority of the cases have been described. From the early days attention has been called to the difficulty of making the distinction between the pulsion and the traction diverticulum and especially Haudek's niche.

[†] Thelemen,²⁴ Glinski,¹⁹ Klob,⁶ Gegenbauer,⁸ Wagner,⁷ Nauwerk,³⁹ Falconer,²⁶ Weischelbaum,⁹ Vigi and Gamberini,⁵³ Muller,²¹ Moynihan,⁶⁷ 2 cases, Heubel,¹⁰ Gardiner,²⁰ Merkel,²³ 2 cases.

It is interesting to note that the first roentgen-ray demonstration of gastric diverticulum was by Brown³⁵ in 1916. Before operation it was considered to be the defect of a gastric ulcer. At operation it was recognized as a pouch-like diverticulum and was invaginated. Four years later Mellon, et al⁴⁰ noticed a defect which was called carcinoma. At operation a diverticulum was found, and section of its mucosa, they state, showed precancerous changes. It was in 1923 that Akerlund⁴² elevated the technic of roentgenologic diagnosis of this condition to its present high plane. Now, under properly controlled conditions, an experienced observer is not apt to label some other condition as a diverticulum. Failure is more liable to occur on the negative side, i.e. diverticula when small, or in unusual positions may not produce recognizable shadows.

Akerlund laid down certain essential requirements to be met before a clear cut decision could be made. The sac must be mobile, it must be loose and unattached to extra-gastric surrounding tissue and organs, the shadow must be well defined, smooth, regular and must be noted from various angles. Generally there is no tenderness.

The cardiac end of the stomach is a loose, rather flabby tissue and occasionally it overhies the fundus, so that to the inexperienced observer the bizarre examples of juxtaposition are puzzling. This type of residual must not be confused with diverticula. It is possible that this is one of the bases for a number of alleged mistaken roentgenologic diagnoses of diverticula of the stomach. I say allegedly mistaken because their absence was inferred from the fact that they were not found at operation. However, as noted in the case report, it seems quite likely that some of the pouch-like type of diverticula may easily be missed at operation, particularly so when they occur in such surgically inaccessible regions as near the cardiac orifice of the stomach.

In spite of the fact that a number of roentgen-ray diagnoses have been corroborated at operation and that numerous undiagnosed diverticula have been seen at autopsy, there is a large school of skeptics. The first of these was de Quervain⁴⁴. He has been followed by Schlesinger,³⁷ Guillot,⁴⁵ Zoltan,⁴⁶ Muller³⁸ and a number of recent Italian investigators. Especially vehement among them are Anziolotti,⁵¹ and Taddei.⁴⁷ The former has written a long review on the subject which contains much of interest and a great deal not germane. It would seem that the only justification for this school is that it draws attention to the care necessary for diagnosis. It also illustrates the need for correct historical approach since its exponents are unaware of the proved cases in the literature.

SYMPTOMS

Many investigators have reported instances in which symptoms were accredited to gastric diverticula. In a number of these studies, diagnosis was made by roentgen-ray. While under properly controlled conditions this is

a satisfactory procedure, it does not rule out other complicating factors which might readily be the basis for the symptoms. Other cases have been reported in which operative procedures have been carried out on patients with definitely known complicating disorders. In some of these instances the diverticulum was found during the routine surgical examination of the stomach.

The only acceptable method for establishing a basis for the belief that diverticula might cause symptoms is by surgery. In uncomplicated cases the disappearance of symptoms, following diverticulectomy, would be fairly conclusive proof if a sufficient number of patients were operated upon. In table 3 is a compilation of the 28 operations performed on patients with ap-

TABLE III
Records of Some of the Findings on 28 Patients before and after Operation

Ref	Author	Age of Patient	Symptoms	Position of Diverticulum	Result
12	Kleine	adult	+	prepyloric	not stated
73	Sinclair	4 months	+	prepyloric	cured
44	Tupper	43	+	prepyloric	cured
56	Southerland	51	+	prepyloric	cured
27	Jones	33	+	prepyloric	cured
57	Weiss	49	+	prepyloric	cured
35	Brown	27	+	prepyloric	cured
40	Mellon et al	54	+	greater curvature mid portion	cured
83	Gile	7	+	prepyloric	
87	Bell and Golden	37	?	cardiac	not found
63	Lawson	50	no	cardiac	not found
33	Boreszky	32	+	prepyloric	cured
33	Boreszky	53	+	prepyloric	cured
61	Thomson	45	+	cardiac	questionable
72	Pansdorf	48	+	prepyloric	cured
13	Kolaezek	45	+	prepyloric	
82	Lenarduzzi	48	+	greater curvature mid portion	not found
90	Bonnet	44	+	cardiac	cured
91	Rivers	36	+	cardiac	cured
		28	+	cardiac	no note
		43	+	greater curvature mid portion	no note
		30	+	prepyloric	no note
		26	+	prepyloric	cured
		51	+	prepyloric	no note
		49	+	prepyloric	cured
		59	+	prepyloric	not cured
55	Delherm	adult	+	prepyloric	cured
48	Stolz	48	+	prepyloric	cured

parently uncomplicated gastric diverticulum. It shows that an impressive number, 64.3 per cent, became symptom free after operation. Three of the operators were unable to locate the diverticulum. In 18 per cent of the cases where symptoms were accredited to the abnormality, no note was given as to the effect of the operation. In the cases of only two of the patients was there doubt that the symptoms were caused by the diverticulum. In all but six of these cases the diverticulum was located in the fundic or pyloric regions.

In a few cases, notably those of Huist and Briggs,⁵⁴ symptoms disappeared after the patients learned to empty their diverticula by postural drainage. Bell and Golden⁸⁷ also state that this procedure might be of assistance.

Judging from the reported cases, the symptomatology is varied and apt to be vague. The most general complaint is indigestion, i.e. gas, distention, eructation and, at times, pain coming on some time after meals. A considerable number of the patients complained of a gnawing sensation and a hunger pain with relief by food which was suggestive of peptic ulcer.

Since it may now be taken for granted that diverticula do cause symptoms, it is quite likely that the symptoms of a number of those patients, whose diagnosis was made by roentgen-ray, were caused by the diverticulum. Many of the cases were carefully studied, and an analysis of the impressions of the investigators shows that in 49 per cent of the cases the opinion prevailed that there was a direct connection between symptoms and sac, and that in 16 per cent of the cases such a connection was held to be questionable.

In table 2 it may also be seen that in 21 cases (about 20.3 per cent) there was no statement as to symptoms and in only 16 cases (about 15.5 per cent) did the writers explicitly state that there were no symptoms. Of the former, 17 were noted in autopsy material in which the diverticulum was an incidental finding and a careful review of the clinical symptoms was not given. Of the latter there are a number of cases diagnosed by roentgen-ray in which the diverticulum was also a chance finding.

Bleeding is not a rare complication, having been noted on eight occasions^{56, 91, 90, 35, 42, 83, 73, 30}. Surgery has been utilized in six of them. In one, evidence of bleeding from a diverticulum was found post mortem. In the other instances it ceased.

It should also be noted that in all the literature no case of rupture of a gastric diverticulum has been reported.

MISCELLANEOUS DETAILS

It may be of interest to recount some of the other peculiarities met with in this abnormality. Four times^{91, 56, 45, 82} it has been noted that there were two or more diverticula of one stomach. In the same number of instances^{12, 26, 91, 14} it has been associated with a diverticulum of the duodenum. On three^{14, 82, 91} occasions a gastric diverticulum was noted in patients with diverticula of the colon.

The combination of diverticulum and ulcers has been commented upon by a number of writers. Kleine,¹² Boreszky,³³ Schlesinger³⁷ and Jones²⁷ feel that diverticula may result from a gastric ulcer when internal pressure reaches a certain height. However, the great majority of diverticula have not been found in association with ulcers. Consequently, whereas the symptoms of uncomplicated gastric diverticula are often suggestive of peptic ulcer, it must not be forgotten that ulcers may be associated with the ab-

normality In the articles reviewed the association of diverticulum of the stomach and peptic ulcer has been encountered 10 times ^{77, 85, 37, 42, 91, 48, 12, 14} Three of the cases were reported by Kleme ¹²

TREATMENT

Treatment of this abnormality, as in most medical problems, is a matter of judgment Probably a number of diverticula have been observed in the study of a patient suffering from neurosis, though the defect was giving no symptoms The living case reported above is an example of this situation and it would be clearly erroneous to consider this abnormality as a cause of his symptoms It is questionable if diet or medication has any useful field of application here However, in certain instances, where there is reflex irritability, some relief may be obtained by smooth food and by belladonna Obviously, if there are no symptoms the conditions should be left alone, for let it be recalled that no report of perforation has come to light Consequently, there is no necessity to make an immediate decision between medical and surgical treatment

The question of carcinoma developing is of course to be considered Here it may be restated that only a minimal number of such cases has been observed Therefore the risk is apparently but slight Instances have been reported in which relief from symptoms was produced by postural drainage, but this procedure would be of service only in those cases having a sufficiently broad pedicle

As noted above, 24 cases have been reported in which the symptoms of the patient have justified operation and in which postoperative relief was obtained Consequently one should not hesitate to use surgery if the occasion warrants it

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A STUDY OF FOUR CASES OF ACQUIRED ARTERIO- VENOUS FISTULA BY MEANS OF THORO- TRAST ARTERIOGRAPHY

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ARTERIOGRAPHY is a valuable adjunct to the methods of investigation of vascular disease of the extremities. Thorotrast,† a 25 per cent stabilized colloidal solution of thorium dioxide, is a very satisfactory medium for this procedure. This radiopaque contrast medium was used first for hepatosplenography^{1,2}. It has been used without apparent serious immediate or remote ill effects by a number of investigators in this country^{3,4,5} in spite of its non-acceptance by the Council on Pharmacy and Chemistry of the American Medical Association⁶. For several years it has been used extensively both abroad and in the United States for arteriography of the extremities^{7,8,9,10,11,12,13}. The amount necessary for arteriography is much less than the 75 cc often employed for hepatosplenography. The use of this amount for the latter purpose in most of 175 cases by Rigler, Koucky and Abraham⁵ over a period of three and a half years and in 200 cases by Yater, Otell and Hussey¹⁴ over a period of nearly five years has not been found to be associated with latent radioactivity, the most important ill effect contemplated. For roentgenographic demonstration of the vascular system of an upper extremity an average of 10 cc and of a lower extremity an average of 20 cc are usually sufficient. These relatively small amounts are certainly devoid of any possible latent ill effects.

TECHNIC OF ARTERIOGRAPHY

With a moderate amount of experience the brachial artery in the antecubital fossa (the needle pointed toward the axilla) and the femoral artery in Scaipa's triangle (the needle pointed toward the pelvis) can readily be entered through the skin with a venipuncture needle (18 gauge, 2 inches long). The skin and tissues around the artery are first anesthetized under aseptic conditions with some local anesthetic, such as 1 per cent novocaine. The artery is punctured by the needle attached to a syringe containing the Thorotrast, the extremity being in position for the taking of the first roentgenogram. When the point of the needle is within the lumen of the artery bright red blood flows forcibly into the barrel of the syringe and pulsates therein until the vessels proximal to the needle are occluded. In the arm the cuff of a sphygmomanometer is usually used for this purpose, the cuff being inflated above the systolic pressure. In the thigh an assistant can

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† Manufactured by the Heyden Chemical Corporation of New York

easily occlude the femoral artery by digital pressure of the vessel against the pubic bone. The Thorotrast, at room temperature or previously warmed, is then injected with moderate speed into the artery and the needle withdrawn. The first roentgenogram, usually anteroposterior, is taken almost at once without allowing blood to flow into the arteries.

If the upper extremity is to be studied the forearm and hand, palm upward and fingers slightly separated, are posed on one half of a 14 by 17 inch roentgen-ray film, the other half being covered by a lead shield. After the first exposure is made the extremity is shifted to the other half of the film. The sphygmomanometer cuff is rapidly deflated to the height of the diastolic pressure and four beats are allowed to pass into the forearm, after which the cuff is rapidly inflated to a point above the systolic pressure. The second exposure is then made. The first exposure usually shows the main arteries of the forearm with a few of their branches and the palmar arches, the second shows some of the main arteries of the forearm, the palmar arches, some of the digital arteries and often some of the veins.

If the lower extremity is to be studied the lower two-thirds or more of the thigh and the upper one-fourth of the leg are posed on half of the film. After the first exposure the film is shifted down to include on the unexposed half the leg and foot either in the anteroposterior position or in the lateral position with the leg somewhat flexed. Five beats are then allowed to pass into the extremity, after which the occlusion is re-applied and the exposure made. The first exposure usually shows well the femoral artery and a few of its branches, the popliteal artery and the first part of its main branches, the second shows the main arteries of the leg with some of its branches and the main arteries of the foot.

The following roentgen-ray technique is satisfactory. Tube distance 30 inches, $\frac{1}{2}$ millimeter aluminum filter, high speed screens, 100 milliamperes, 2/10 second, voltage varied according to thickness of the part (3 cm, 46 K V P, 4 cm, 47 K V P, 5 cm, 49 K V P, 6 cm, 52 K V P, 7 cm, 55 K V P, 8 cm, 57 K V P, 9 cm, 59 K V P, 10 cm, 62 K V P, 11 cm, 65 K V P, 12 cm, 68 K V P, 13 cm, 71 K V P, 14 cm, 74 K V P, 15 cm, 76 K V P).

One of the most important difficulties occasionally encountered is spasm of the artery consequent to its puncture. To avoid this drawback I make it a custom to inject the contents of an ampule of Spasmalgim* intravenously about 15 minutes prior to the arterial puncture. This procedure also relieves the nervous patient's apprehensiveness.

When properly performed, the injection of the Thorotrast is made with light pressure. If the injection requires undue pressure the needle is not in the lumen of the artery. Even if the medium is injected into the tissues about the artery or into the wall of the vessel, however, no serious damage

* Each ampule contains Pantopon 0.011 gm, papaverine hydrochloride 0.022 gm and Atromal (sulphuric acid ester of atropine) 0.001 gm. It is prepared by Hoffmann-LaRoche, Inc.

is done. There are, however, pain, redness and local heat, which subside in a very few days with the use of hot, moist compresses.

USES OF ARTERIOGRAPHY

Arteriography has been used mainly to assist in determining the kind of vascular disease, the location of occlusions and the extent of the collateral circulation^{12, 13, 15}. Consequently, most of the cases have been instances of vascular disease associated with trophic changes or gangrene. Some cases have been reported, however, of aneurysm and arteriovenous fistula. The latter have been rare. Horton has reported a case of acquired arteriovenous fistula¹⁶ and one of congenital fistula¹⁷. Frick and Levy¹⁸ have reported two cases of the congenital form.

ACQUIRED ARTERIOVENOUS FISTULA

The acquired form is usually due to a gunshot or stab wound, more often the former. There is usually one fistula, but occasionally there are more. The penetrating body must go through both the artery and the vein. A hematoma forms about the vessels, soon stopping the hemorrhage. Adhesions develop about the outer surfaces of the vessels, closing their lateral wounds, but the blood from the artery, being under much higher pressure than that in the vein, passes through the fistula between the artery and the vein and prevents closure of the adjacent openings. Thus, the individual bleeds constantly into the veins of the extremity. The fistula is usually a direct one, the formation of an aneurysmal sac between the artery and vein being uncommon. Medium-sized and large vessels are usually affected, since the penetrating object must pass through them without completely severing them.

A small fistula is well borne by the organism, necessitating little readjustment, but a large one involving a large artery and vein calls forth compensatory mechanisms in order to overcome the effect of the constant tendency to a diminution of arterial blood volume and to provide sufficient blood flow through the affected extremity. The heart enlarges and beats faster, the pulse pressure increases, due mainly to a drop in the diastolic pressure, and the total volume of blood increases. When the fistula is closed by compression the pulse rate suddenly drops to normal (Branham's bradycardiac sign¹⁹), the blood pressure becomes raised, and the cardiac shadow contracts. Because of the severe strain placed upon the heart, congestive failure may eventuate.

The local effects consist in dilatation of the vein involved and the proximal part of the artery. The tributary veins become dilated and tortuous. The superficial veins of the extremity become prominent. The blood pressure in the veins of the extremity approaches that of the arteries, and the oxygen content of the blood in the veins becomes practically arterial. The veins may actually pulsate. The surface temperature over the fistula is

usually increased, that distal to it decreased. The limb distal to the fistula is often increased in girth due to venous engorgement and edematous infiltration and hypertrophy of the subcutaneous connective tissue with atrophy of the skin and skeletal muscles. Trophic changes are prone to occur distal to the fistula. Since the flow of blood through the arteries distal to the fistula is greatly decreased, the veins take over the function of the arteries in nourishing the limb, but there is difficulty in the return of deoxygenated blood from the capillaries. Partial anoxemia of the tissues results. If these tissues are even slightly injured the normal inflammatory reaction of repair is feeble or absent, and progressive ulceration or gangrene supervenes.

A loud hum with systolic accentuation is heard with the stethoscope over the fistula and in its neighborhood and is transmitted down the course of the veins, often to the tips of the fingers or toes. A thrill is palpable also over the fistula and may be transmitted a short distance along the vein.

There is usually no difficulty in differentiating between a simple aneurysm and an arteriovenous fistula, since the physical signs mentioned above are lacking except perhaps for a less intense systolic murmur, and a thrill if present is less marked. Trophic disturbances are not so common or severe. The venous phenomena do not occur, and the oxygen content of the blood in the veins is not increased.

The four cases reported below illustrate the phenomena described. They also show the value of arteriography in cases of arteriovenous fistula. The exact site of the fistula may be determined, its size estimated, and the mechanism of blood flow through the extremity explained. The extent of the collateral circulation, however, can not thus be gauged.

CASE REPORTS

*Case 1 Small fistula between the ulnar artery and vein.** A negro boy, aged 15 years, was sent to the Gallinger Municipal Hospital on February 26, 1933 because his heart had been found to be moderately enlarged by a physician in the syphilis clinic, where he was being treated because of a positive blood Wassermann reaction. His health had always been good except for measles, mumps and chickenpox. Five months previously he had been wounded in the right arm by a shotgun. His arm had become swollen and bluish immediately afterward, but these signs had gradually disappeared without leaving any disability of the extremity. Physical examination was essentially negative except for the heart and the right arm. The heart was moderately enlarged, the apex beat being 8.5 cm from the midsternal line in the fifth left intercostal space. There was a soft systolic murmur at the apex and a higher pitched systolic murmur at the base. The second aortic sound was accentuated. The right arm and forearm were visibly larger than the left. The length of both arms was 48 cm. The circumferences of the arms at various points were as follows: Arm, 7 cm above olecranon process 22 cm left, 23.8 cm right. Forearm just above wrist 15.2 cm left, 16 cm right. Hand below thumb 20 cm left, 20.4 cm right.

A number of small scars in the antecubital fossa and its neighborhood were present where the buckshot had entered. The movements of the extremity were normal. Trophic lesions and color changes were not noted, and the superficial veins were not dilated. A loud humming sound with systolic accentuation was heard with

* Previously reported by Yater and White²⁰



FIG 1 *Case 1* Small arteriovenous fistula between the ulnar artery and vein. Many buckshot are present in the tissues about the elbow. A small saccular bulge in the ulnar vein at the site of the fistula is shown on the ulnar side of the forearm. Arteries are visible above and below the fistula, but of the veins only the brachial is visible.

the stethoscope in the right side of the neck and down the entire length of the right arm. It was audible even at the tips of the fingers. The greatest intensity of the murmur was in the antecubital fossa nearer the ulnar side. A thrill was palpable in the extremity, but its distribution was not as great as that of the bruit. Its point of maximum intensity was much more definite than that of the murmur, being about 5 cm below the middle of the antecubital fossa on the ulnar side. The heart rate was 80 per minute, and the rhythm was regular. The systolic blood pressure was 140 mm Hg and the diastolic 80 mm Hg in the left arm, in the right arm the systolic pressure was also 140 mm Hg, but the diastolic pressure could not be determined, the sounds being heard loudly down to the zero point. Closure of the fistula by compression over the point of maximum thrill did not alter the pulse rate appreciably, but the systolic blood pressure in the left arm dropped to 130 mm Hg. The Kahn test of the blood was 4 plus, hemoglobin, 88 per cent (Newcomer), leukocytes, 5200 per cu mm. The urinalysis was normal. Determination of the oxygen content of the blood in the superficial veins of the right arm showed that the blood was practically arterial. A roentgenogram of the chest revealed moderate enlargement of the heart.

An arteriogram was made by injecting 10 cc of Thorotrast into the brachial artery at about its middle (figure 1). Because of the high puncture point a tourniquet was used instead of a sphygmomanometer cuff to occlude the vessels above. A large number of buckshot were shown in the tissues about the region of the elbow. The brachial artery and the arteries of the forearm were well demonstrated, especially the radial and the interosseous. A moderate number of smaller arteries were shown. On the ulnar side of the forearm a short distance below the elbow joint there was a small rounded shadow representing a localized saccular dilatation of the ulnar vein at the site of the fistula. The veins below this point were not demonstrable, but the brachial vein above the elbow was quite obvious. The fistula was apparently one connecting the first part of the ulnar artery and vein. The ulnar artery itself at that point could not be clearly seen because of the presence of buckshot, nor was it possible to say positively that any of the small arteries running downward from this region was the ulnar. They appeared to be more probably muscular branches of the radial artery.

Since it was thought the cardiac enlargement was due to the fistula, operation was advised but was refused. The boy was examined again three years later. He was in excellent health, and there was no appreciable change elicited in the physical examination. Operation was again refused.

Comment Although it seemed that the increased size of the heart was due to the fistula, the fistula was undoubtedly a very small one. To begin with, the affected vessels were relatively small. There was little change in the circulatory status when the fistula was closed. The bruit and thrill of a small fistula are just as intense as those of a large one, sometimes more, so that these signs may not be used as indicators of size. The arteriographic features indicating a small fistula were (1) that the veins were not demonstrated below the sac, (2) the sac was small and localized, and (3) the arteries both above and below the fistula were well shown.

Case 2 Small fistula between the popliteal artery and vein The patient, L. D., a negro aged 44 years, was admitted to the Gallinger Municipal Hospital on July 18, 1935, complaining of chills, fever and pain in the lower right axillary region, which he claimed had begun suddenly about 24 hours before. For about a year he had had a productive cough, increasing weakness, night sweats, low grade fever, occasional

diarrhea, occipital headaches, some loss of weight, vertigo, tinnitus, palpitation of the heart and some dyspnea on exertion. He had been shot with a shotgun in the right popliteal region in 1907. He had had pneumonia, gonorrhea, a chancre and typhoid fever. He did not appear to be very ill. Physical examination was essentially negative except for evidence of pneumonitis in the lower part of the right lung, moderate enlargement of the heart with a blowing systolic apical murmur, and the following findings in the right lower extremity. The latter was larger than the left, having a circumference about 1 cm greater both above and below the knee. A marked systolic thrill was palpable whose greatest intensity was in the right popliteal fossa, but which was felt half way up the posterior surface of the thigh and half way down to the ankle. A loud, harsh bruit was heard with the stethoscope in the popliteal fossa and was transmitted up the posterior surface of the thigh to the back and abdomen and down the leg to the plantar surface of the foot and to the tips of the toes. This was practically continuous, with systolic accentuation. Both thrill and bruit ceased when the femoral artery was compressed above Scarpa's triangle. The blood pressure in the arms was 180 systolic and 100 diastolic. In the right thigh it was 248 systolic and 100 diastolic, while in the left it was 220 systolic and 120 diastolic. The temperature was 102° F, the pulse rate was 120 per minute and the respiratory rate was 26 per minute. Urinalysis was normal. The hemoglobin was 75 per cent, the erythrocytes numbered 3,760,000 and the leukocytes 18,000 per cubic millimeter of blood with 63 per cent polymorphonuclear leukocytes and 18 per cent band forms. The Kahn test of the blood was negative. A roentgenogram of the chest showed a small area of opacity in the right apex and an irregular area of increased density in the basal portion of the right lung. The temperature continued to be elevated a degree or two each afternoon, but the symptoms were soon greatly relieved by bed rest. Attention was then focused on the arteriovenous fistula of the right popliteal artery and vein.

The blood pressure gradually dropped, and on July 25 it was 134 systolic and 84 diastolic in the arms, 180 systolic and 90 diastolic in the right thigh, and 164 systolic and 90 diastolic in the left thigh. With compression over the arteriovenous fistula the blood pressure rose to 148 systolic and 100 diastolic in the arms and to 170 systolic and 110 diastolic in the left thigh. At the same time the pulse rate dropped from 95 to 88 per minute. The venous pressure rose from 86 mm to 110 mm of water. The blood volume as determined by the Congo red test was 5800 cc. The circulation time as determined by the saccharine test was 14 seconds. Blood from a vein in the right thigh was bright red.

Roentgenograms of the middle of the right lower extremity were made after the injection of 20 cc of Thorotrast into the right femoral artery in the region of Scarpa's triangle, with the artery occluded just above by the fingers of an assistant. Although the artery and not the vein was injected, as indicated by the pulsations in the syringe after piercing the vessel, and although closure of the artery above the point of injection was maintained by pressure, it was mainly the veins that were demonstrable in the films (figure 2). The femoral and popliteal veins were greatly enlarged, more especially in the knee, and just below the joint there was a saccular down-pouching of the popliteal vein. Part of the great saphenous vein was visible above the knee. The popliteal vein just below the fistula was seen and also some of its small muscular tributaries, but all were of small size and not tortuous. In the upper part of the film a few small arteries were also noted (not shown in the photograph). Some scattered buckshot were present in the tissues. On another day the injection was repeated (figure 3). The first roentgen-ray exposure was made a trifle later than on the former occasion. The appearance was essentially the same, except that the femoral vein was not visible, but the great saphenous vein, which anastomoses freely with the popliteal vein, was well shown.

On August 13 an operation was performed to remove the segment of the popliteal artery and vein including the fistula. It had been assumed that the collateral circulation was well developed because of the great age of the fistula. But in spite of all postoperative precautions gangrene of the stump followed, and the right leg was



FIG 2 Case 2 Small arteriovenous fistula between the popliteal artery and vein. No arteries are visible. The femoral vein is distended, the popliteal vein is greatly distended and presents a rounded saccular bulge below the knee. The part of the popliteal vein below the fistula is small. Part of the great saphenous vein is shown near the femoral vein. Buckshot are present in the tissues.

amputated above the knee on August 25. However, infection developed in the stump, followed by septicemia, and death occurred on September 21.

Examination of the segment of the popliteal artery and vein containing the fistula showed that both vessels were moderately enlarged and thickened. The fistula was small, admitting only a small probe. The venous sac which had been demonstrated in the roentgenograms was not evident in the empty vessels. Apparently it was not an anatomical sac but merely a dynamic or functional one which existed only during life.

The pulmonary condition for which the patient was hospitalized did not progress during the period of hospitalization. Actually, the pneumonitis of the right lower lobe resolved, as indicated by physical examination and roentgenograms of the chest. The patient's cough subsided but returned a few days before death. Several ex-

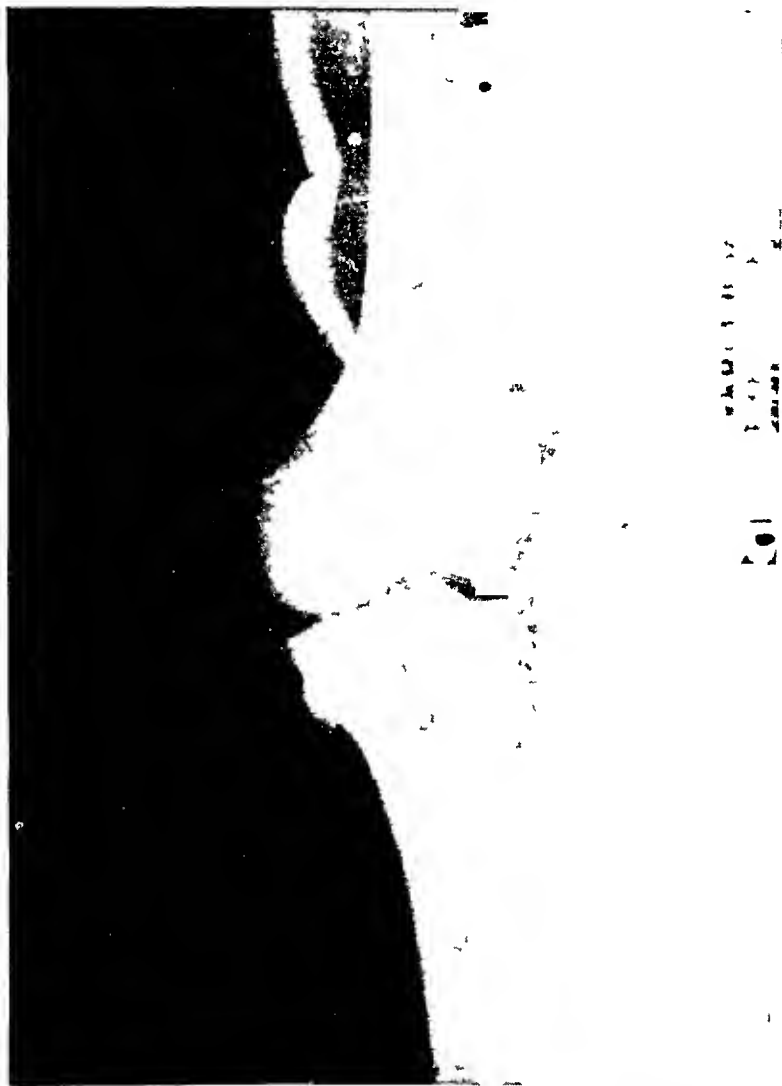


FIG 3 Case 2. Another film after a second injection of Thorotrast. The contrast medium has left the femoral vein and fills mainly the great saphenous vein and the popliteal vein.

aminations of the sputum failed to reveal tubercle bacilli. Permission for necropsy could not be obtained because the patient had no known relatives.

Comment Although the arteriograms in this case were not essential to the diagnosis of arteriovenous fistula nor to the determination of the location of the fistula, and although mistakes in judgment were made, interesting information was obtained from the experience afforded by the case. As Allen and Camp¹³ have stated, arteriography is valuable in increasing

our knowledge of the mechanics of vascular diseases. In the case here reported it is seen that the force of arterial blood passing into a vein through a small opening may produce during life a localized dilatation in the vein which roentgenographically resembles an aneurysmal sac but which is not a true aneurysm. The small size of the fistula was demonstrated arteriographically by the absence of dilated and tortuous veins distal to it. The absence of arterial shadows shows how rapidly blood flows from the artery into the vein even through a small fistula, but in the case of a small fistula apparently most of the blood entering the vein through the fistula returns immediately toward the body and relatively little goes into the veins of the limb distally.

The great age of the fistula without evidence of chronic passive congestion in this case was an indication of its small size. The cardiac hypertrophy was due probably more to hypertension than to the fistula. A small fistula is not necessarily conducive to the development of an adequate collateral circulation, even after many years of existence. In fact, it is impossible on the basis of arteriographic studies to determine whether a fistula of any size stimulates the formation of a very adequate collateral arterial circulation, although in all other vascular diseases of the extremities the extent of the collateral circulation is one of the most important uses of arteriography. However, Reid,²¹ on the basis of clinical and experimental studies, concluded that an arteriovenous fistula is the most powerful stimulus there is to the development of collateral circulation of the surrounding vessels. Nevertheless, it is safer to assume in any case of arteriovenous fistula that the collateral circulation is not adequate, and measures to assure an adequate collateral circulation should be instituted before operation. Such measures consist mainly in the daily occlusion of the artery leading to the fistula for a few weeks prior to operation. Increasing periods of occlusion from five to fifteen minutes one to several times a day should be instituted. Had this procedure been followed in this case the patient's limb and life might have been saved, although it is well known that ligation of the popliteal artery is fraught with more danger than that of the femoral artery higher up.

Case 3. Small fistula between the femoral artery and vein. A white man, G. B., aged 34 years, entered Georgetown University Hospital on January 7, 1936, complaining of weakness, dyspnea on exertion, pallor, nocturia, and swelling of the ankles. The illness had apparently begun about 10 months before with intermittent pains in the right side of the body from the shoulder to the hip, present mainly on exertion. After several months these had ceased. Much later the other symptoms had become noticeable. The past history was unimportant except for a shotgun wound in the left thigh when the patient was eight years old. About three weeks later he had noticed a palpable thrill just distal to the left inguinal ligament. About seven years later arteriovenous aneurysm was diagnosed on the occasion of a fracture of the left hip. On admission he was found to be poorly nourished, pale and weak. The heart was slightly enlarged, and there was a loud systolic apical and precordial murmur. The blood pressure was 132 systolic and 56 diastolic. Numerous small scars were

present in the skin of the upper, anterior part of the left thigh. There were visible strong pulsations of the femoral artery in Scarpa's triangle with slight bulging in that region. A strong thrill was palpable in the same area. A loud systolic murmur was audible from the umbilicus to the tips of the toes, with greatest intensity over the femoral artery just below the inguinal ligament. There were no trophic changes, and there was very little difference in the measurement of the lower extremities. With pressure over the apparent site of the fistula the pulse rate instantly dropped from 98 to 90 per minute, the venous pressure rose from 72 to 174 mm. of water, and the blood pressure fell 10 mm. Hg. The blood pressure in the left leg was 140 systolic and 68 diastolic and in the right leg 124 systolic and 64 diastolic. The urinalysis showed some albumin and a few casts. The hemoglobin was 28 per cent (Newcomer), the erythrocytes numbered 1,980,000 and the leukocytes 6,800 per cubic millimeter of blood, with 68 per cent polymorphonuclear neutrophils. The blood non-protein nitrogen was 45 mg. per 100 c.c. of blood. The phenolsulphonephthalein test of renal function showed 12 per cent elimination of the dye during the first hour and 18 per cent during the second hour. The Kahn test of the blood was four plus. The temperature was elevated irregularly daily to 101.5 to 103° F. with occasional morning remissions to normal. The pulse rate varied from 100 to 130 per minute.

An arteriogram was made with some difficulty, since the fistula was apparently so high in the thigh that the femoral artery had to be injected close to the inguinal ligament and therefore close to the point where the assistant occluded it. Furthermore, firm compression at this point was quite painful. However, a fair arteriogram was obtained (figure 4). Shadows of many buckshot were seen in the tissues of the upper thigh. There were no arteries definitely visible. A large, somewhat oval and mottled shadow of the dilated upper part of the femoral vein was visible. Below this on the medial side of the femur were the main vein and a moderate number of small veins, not very tortuous. On the lateral side of the femur other straight veins were evident.

Subacute bacterial endocarditis was considered a probable diagnosis in spite of persistently negative blood cultures, but on reflection it was deemed possible that the vegetations might be present in the arteriovenous fistula and not in the heart, as in the case of Hamman and Rienhoff²². Accordingly, it was decided to attempt extirpation of the fistula, but only after a period of daily occlusions of the femoral artery to stimulate the development of collateral circulation, even though the fistula was considered to be small and had existed 26 years without evidence of heart failure or trophic changes. During this preparatory period evidence of increasing renal insufficiency developed, the blood non-protein nitrogen rising to 70 mg. per 100 c.c. of blood.

On January 29 operation was performed by Dr. Fred Sanderson. The fistula was found to be located about 2 cm. below the origin of the profunda femoris artery, which like the common femoral artery was very large. The femoral vein was greatly dilated in this region. There were many vessels in the vicinity, mainly veins, and the operation was difficult. The segments of the femoral artery and vein containing the fistula were extirpated. In order to control hemorrhage it was unfortunately necessary to ligate the great saphenous vein, and a hemostat had to be left on a tributary vein. Examination of the specimen removed showed a fistula about 2 mm. in diameter connecting the artery and vein directly and containing no vegetations.

After the operation the arteries of the leg and foot were still felt to pulsate, and the extremity remained almost as warm as the other. However, the limb swelled a great deal and became somewhat livid because of venous obstruction. The day following the operation a diastolic murmur became audible over the base of the heart for the first time. A day later petechiae first appeared. Hiccough began and persisted. The operative wound became infected. Ten days after the operation profuse venous hemorrhage occurred from the wound, and a few hours later the patient died.



FIG 4 Case 3 Small arteriovenous fistula between the femoral artery and vein. No arteries are visible. The upper part of the femoral vein is greatly dilated. Below this fusiform venous aneurysm the veins are visible but are not tortuous. Many buckshot are present in the tissues.

Necropsy revealed bacterial vegetations on the aortic valve but no evidence of chronic endocarditis. The femoral vein was completely thrombosed. There was ulceration of the profunda femoris artery, and a small communication with the vein had resulted from this lesion.

Comment The fistula was small and had existed for years, but some part of the arterial blood to the affected extremity apparently passed into the veins through the fistula, although a goodly part also went down the profunda femoris artery. The direct course of the veins instead of a tortuous one indicated that the fistula was small. If it had not been necessary for controlling hemorrhage to tie the great saphenous vein the fistulectomy would undoubtedly have been successful, since the fistula was just distal to the origin of the profunda femoris artery. However, the venous return was obstructed and thrombosis occurred in the veins, resulting in severe venous stasis in the limb. The foot remained warm and the arterial pulsations were present.

*Case 4 Large fistula between the popliteal artery and vein** The patient, G K, a negro aged 52 years, had been shot in the region of the left knee with a 0.38 caliber rifle in 1921, 14 years before. The bullet entered the skin just below the patella on the anterolateral aspect of the leg and came out in the lower popliteal region. In three or four days the leg became greatly swollen from the knee down. It had remained almost as large from that time but was always less swollen after a period of bed rest. An ulcer had appeared about a year later on the middle of the anterior aspect of the leg. This had become quite large but some healing had occurred from time to time. The toe nails of the left foot had become thickened and had not grown as fast as those of the right foot. For the previous five years there had been intermittent bleeding from the rectum of variable amounts of bright blood. Some dyspnea on exertion had been noticed latterly.

The essential points of the physical examination were as follows. The heart was moderately enlarged, the visible apex impulse being 10.5 cm from the mid-sternal line (the clavicle measured 18 cm). There was a systolic precordial murmur. A strong pulsation synchronous with the heart beat was palpable in the left lower quadrant of the abdomen. The left leg was considerably larger than the right below the knee. The measurements were as follows:

Circumference, middle of thigh, right—43 cm, left—41.8 cm

Circumference of calf, right—31 cm, left—37.3 cm

Distance from anterior superior iliac spine to internal malleolus, right—97.5 cm, left—100 cm

A large area on the anterior and lateral surfaces of the left leg was deeply pigmented, and there was a small, irregular granulating ulcer in its middle (figure 5). The left ankle was limited greatly in its movement. The left foot was red, very moist and quite warm. The superficial veins were prominent over the left thigh and upper calf, and the great saphenous vein was very large (about 2 cm in diameter) from just below the knee up nearly to Scarpa's triangle (figure 6). Blood drawn from this vein was as red as arterial blood. The femoral artery was seen to pulsate extremely in the upper part of the thigh, and could be occluded with the fingers with difficulty. The popliteal artery also pulsated greatly. A strong thrill was palpable in the popliteal fossa and radiated upward and downward for several inches. A very loud, almost continuous bruit with systolic accentuation was audible with greatest

* Case of Dr. Paul Putzki at Providence Hospital.

intensity in the popliteal fossa, but could easily be heard down to the tips of the toes and up to the umbilicus

The pulse rate was 92 per minute, and on occlusion of the popliteal artery by compression it dropped immediately to 64 per minute. The blood pressure in both arms was 130 systolic and 60 diastolic with the fistula open and 150 systolic and 80



FIG 5 Case 4 Large arteriovenous fistula between the popliteal artery and vein
Affected leg enlarged, pigmented and ulcerated

diastolic with it closed. The blood pressure in the left thigh was $300 +$ systolic and 60 diastolic. In the right thigh it was 190 systolic and 120 diastolic with the fistula open and 220 systolic and 130 diastolic with it closed. The venous pressure in the right antecubital vein was 68 mm of water with the fistula open and the same with it closed. In the right saphenous vein it was 84 mm, in the left it was 160 mm, and

the column oscillated with the heart beat. The circulation rate with the saccharin test was 31 seconds when the fistula was open and 23 seconds when it was closed. Thermographic studies showed an increase of temperature of the skin in the left popliteal space, but very little change elsewhere in the affected limb.

Studies of the rectum did not reveal any intrinsic lesion, and it was thought that



FIG 6 Case 4 Great saphenous vein greatly dilated

the pulsations in the left lower quadrant of the abdomen were due to dynamic pulsation of the iliac artery on that side and that the bleeding was due to venous engorgement about the rectum.

Two series of arteriograms were made on different days. The first time 25 c c of Thorotrast were used, but due to the large size of the venous bed in the extremity the shadows were not as dense as usual. The second time better detail was shown by the injection of 50 c c. Several films were taken in succession as rapidly as pos-

sible, one beat being allowed to go down the limb between films (figures 7 to 10). The only arteries visible were some small ones high up in the thigh. In the first film the popliteal vein was seen to be greatly distended and some of its tributaries filled, the great saphenous vein with one of its branches was visible (figure 7). In the second film the popliteal vein appeared to be even larger and more of its tributaries



FIG 7 Case 4 Large arteriovenous popliteal fistula. Film number 1 of a series. The popliteal vein is greatly dilated and forms a pouch below the knee. The great saphenous vein is visible. Tributary veins are very tortuous.

in the leg were visible, resembling large round worms, there was also a long, coiled vein in the thigh, but the saphenous vein was no longer evident. The third film was essentially the same, but the veins in the calf were more prominent (figure 8). In the fourth film there was just a dim shadow of the popliteal vein, but the veins in the calf were very numerous, and more small veins were visible in the thigh (figure 9). The fifth film showed the small veins very indistinctly, but the femoral and saphenous

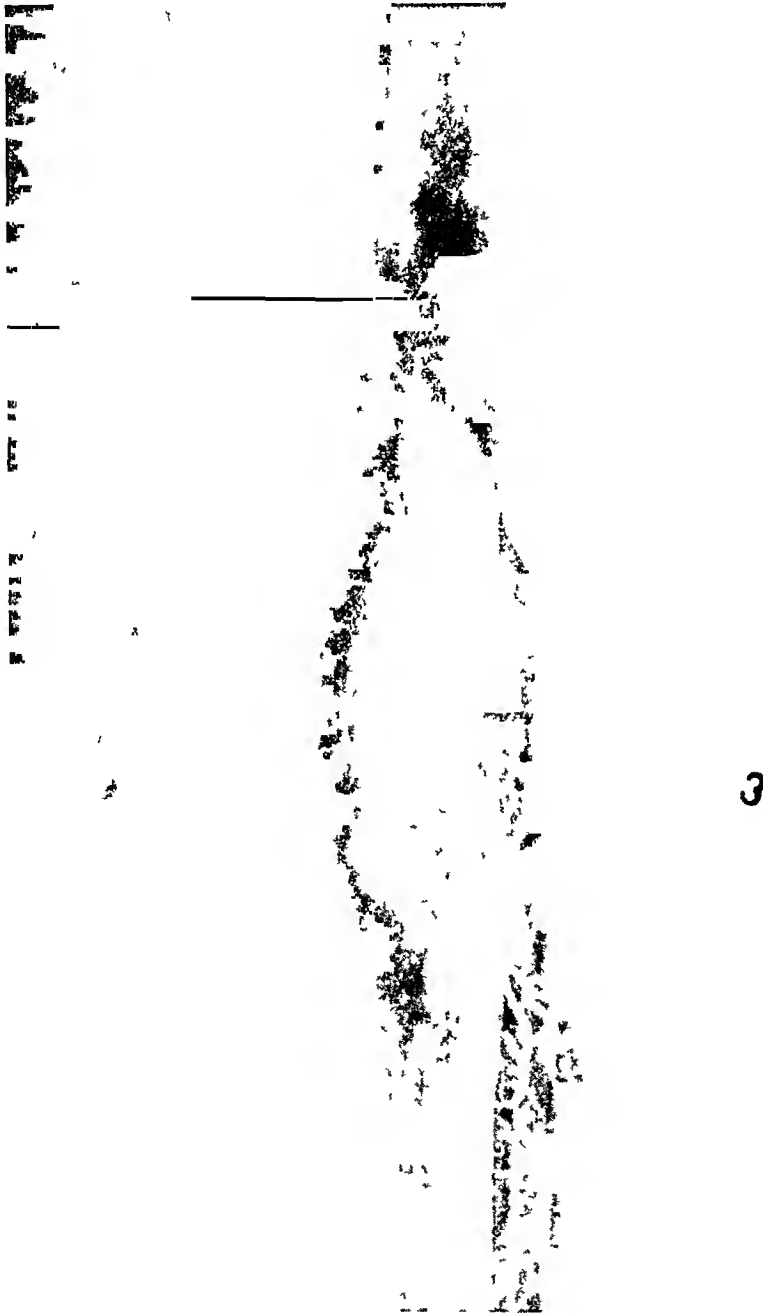


FIG 8 Case 4 Film number 3 The great saphenous vein is no longer visible. Many coiled veins are visible below the knee.

veins were visible, although they were not as dense as originally (figure 10) The sixth film was quite similar The roentgenograms also showed enlargement and evidence of osteitis of the tibia and fibula

The patient was kept in the hospital several weeks and daily occlusion of the femoral artery performed The leg became smaller and the ulcer healed Before operation was contemplated the patient secretly left the hospital



Fig 9 Case 4 Film number 4 The veins in the thigh are barely visible Those in the leg are still readily apparent

Comment This was a case of a large fistula which had existed 14 years without congestive heart failure. Trophic changes were prominent. Practically all of the blood below the knee went through the veins, which ap-



FIG 10 Case 4 Film number 5 The popliteal and great saphenous veins are again evident. The veins below the knee are barely visible.

parently assumed the function of arteries in nourishing the tissues. This function was insufficient because of difficulty in the return of deoxygenated blood from the limb. The arteriograms indicated that the deoxygenated blood left the leg slowly by the same veins through which it entered. Ap-

parently there were two simultaneous, opposite currents in the veins below the fistula

CONCLUSIONS

The following points may be determined by arteriography in cases of arteriovenous fistula (1) the site of the fistula, (2) the size of the fistula, and (3) perhaps the mechanism of the circulation in the limb below the fistula

The site is indicated by the point of greatest bulge in the affected vein, which frequently just below the fistula forms a rounded saccular pouch

The size of the fistula is shown by the degree of visibility of the arteries in the films, by the size of the large veins, and by the number and tortuosity of the smaller veins, particularly those distal to the fistula. In cases of small fistula the arteries may be visible and there are no or relatively few veins visible below the fistula. The few small veins that may be visible are not tortuous. Even in the case of a small fistula between larger vessels the arteries may not appear in the films. In cases of large fistula the arteries are probably never visible, but the large veins are prominent, and the small veins, especially those distal to the fistula, are enlarged, seemingly increased in number and very tortuous.

When the fistula is large the veins distal to the fistula must assume the function of arteries. The return of deoxygenated blood from the limb below the fistula apparently occurs through the same veins down which the arterial blood passes.

The extent of the collateral circulation in cases of fistula is very difficult to judge from arteriograms, since with larger fistulae the arteries are not visible. It is safest to assume in every case of arteriovenous fistula that the collateral circulation is not sufficient and to institute measures to assure an adequate collateral circulation before the operation is performed. In arterial diseases of the extremities, on the contrary, the extent of the collateral circulation can be rather accurately determined by the aid of arteriography.

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EFFECTS OF GASTRIC AND INTESTINAL HYPERPERISTALSIS ON THE ELECTROCARDIOGRAM AS DEMONSTRATED BY SIMULTANEOUS MECHANOGRAMS AND INDIRECT AND SEMIDIRECT ELECTRIC LEADS *

By I HARRISON TUMPEER, S M , M D , *Chicago, Illinois*

REGISTRATION of gastric and intestinal hyperperistalsis on the electrocardiogram has been reported in a previous study ¹ The sources were the gastric activity in a baby with congenital hypertrophic pyloric stenosis and the intestinal contractions in a child with congenital hypertrophic dilatation of the colon (Hirschsprung's disease), and in an elderly adult in whom borborygmi occurred in the course of a routine electrocardiogram Hyperperistalsis was visible in the first two conditions and audible in the last

The peristaltic effect upon the electrocardiogram is not even considered in such a review as Esler and White's ² nor is it mentioned in Mortensen's ³ study of abnormal electrocardiograms The influence of such smooth muscle activity seems entirely ignored although suggestive effects are present in some of Wenckebach and Winterberg's ⁴ observations on the effect of vagus pressure and in a group of routine tracings from the Heart Station of Michael Reese Hospital examined by the author Alvarez and his co-workers ^{5, 6, 7} have reported electrical registration of peristalsis in man and animals In the latter simultaneous mechanograms were submitted Richter ⁸ has demonstrated electrogastrograms of the exposed stomach in etherized dogs, and more recently Hasama ⁹ studied the pendulum peristalsis in the small intestines by direct electrodes Puestow ¹⁰ worked with isolated intestinal loops and muscle strips obtaining electrical and mechanical records Berkson ¹¹ as well as Puestow demonstrated that these effects maintain their relationship even after the tissue has been isolated from the central nervous system, indicating an intrinsic mechanism controlling peristalsis Nevertheless, no previous observations on simultaneous electrical and mechanical phenomena have been demonstrated in the intact human subject The present study was undertaken to record objectively the simultaneous mechanical and electrical registrations during gastric and intestinal hyperperistalsis

THE PRESENT STUDY

Gastric hyperperistalsis was studied in an adult male with pyloric obstruction and marked visible peristalsis

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From the Sarah Morris Hospital for Children and the Heart Station, Michael Reese Hospital, Chicago

With the technical assistance of Bessie Phillips, Electrocardiographic Technician, Heart Station, Michael Reese Hospital, Chicago

CASE REPORT

E R, male, 42 years old, was admitted to the Michael Reese Hospital, medical service of Dr Wm C Buchbinder, September 21, 1934, with the admission diagnosis of pyloric obstruction due to duodenal ulcer, and signed his own release because he refused surgical treatment, October 5, 1934. His symptoms had begun two years before with postprandial, peri-umbilical pain occurring one or two hours after meals, associated with a sensation of weakness and nausea, and more recently with vomiting at the onset of the pain. He had vomited food eaten one or two days previously. Vomiting had increased in frequency so that recently he dared not eat a meal but nibbled small amounts of food continuously. Earlier in the course of the illness the Sippy regime had been prescribed at another institution but appeared to aggravate the symptoms. One year ago baking soda had given slight relief, but in the past few months it had increased his distress by the resulting gas formation. The pain has sometimes been relieved by cold milk, and always by vomiting. He awakened three to five times nightly. He had lost seven pounds in the preceding six months and three in the preceding two weeks. For the past two months he had felt weaker, and recently had vomited practically everything, he had been continuously hungry but could not eat. There had been no bowel movement for three days before admission.

Physical examination revealed a poorly nourished, white male, not acutely ill. The chief finding was marked epigastric peristalsis with gurgling and splashing sounds when the upper abdomen was tapped. As much as 2000 cc of gray brown liquid were aspirated in a series of frequent gavages. The blood picture, blood sugar, non-protein nitrogen and urine were within normal limits. Blood pressure was 108 to 112 systolic and 84 to 72 diastolic.

Fluoroscopic Report "Stomach contains a considerable amount of residual fluid. The fundus is dilated, and the walls reveal marked peristalsis. Definite antral and pyloric spasm is present. Tenderness is elicited over the pylorus. There is 80 per cent retention in five hours. The duodenal cap does not fill immediately, and is markedly defective when filled in one-half hour."

Roentgenographic report "The film confirms the fluoroscopic findings, revealing a pyloric obstruction and a defective cap. Whether the cause of obstruction is duodenal or pre-pyloric is not revealed owing to the pronounced pylorospasm."

Study A Lead III was taken on the patient with a slowed camera. The mechanical registration was accomplished by air pressure effects on a Frank capsule¹² to whose rubber diaphragm a tiny mirror was fastened throwing a beam of light on the slit in the camera of the electrocardiograph so that both electrical effects by means of Lead III and mechanical effects could be registered on the film simultaneously. In this part of the study the patient swallowed the usual stomach balloon which was attached by rubber tubing to the Frank mirror-holding capsule. (Figure 1)

Comment The undulation in the base line of the electrocardiogram occurs with the passing of the peristaltic wave usually beyond the mid line. It is not an artefact and resembles the kymographic record of a peristaltic wave. This has been pointed out by Alvarez and myself. The excursions differ from the kymographic record because the rapidity of the film distorts the picture by widening and flattening the curves. The black band tracing is the result of changes in the pressure of the stomach balloon and represents only crudely, as will be explained, the mechanogram of the stomach. The

superimposed low excursions in the latter occurring about every three to four seconds demonstrate nicely the respiratory effect

If the longer excursions are examined it will be noted that a slow rise of the balloon record usually accompanies the undulation in the electrocardiographic base line. This, then, is the first reproduction of simultaneous electrogastragrams and mechanogastragrams. However, there can be no



FIG 1 Simultaneous electrogram by Lead III and mechanogram by stomach balloon. Note shift in base line of electrocardiogram accompanying balloon tracing. Note also minor respiratory and cyclic cardiac fluctuations.

identical parallelism because the electrocardiographic excursion by this method does not begin until the visible peristaltic wave has crossed the fundic portion and traverses the mid line, a fact previously noted. In other words, the peristaltic wave can be seen moving across the left hypochondrium to the right even without photographic confirmation, but the actual deflection in the electrocardiographic base line does not appear until the mid line has been crossed, probably because of the nature of the summation of the stresses. Furthermore, absolute parallelism of electro- and mechanograms by the balloon method is only exceptionally achieved because the mechanical method has a lag and for other reasons gives only a crude reproduction of stomach activity. First, the balloon is never large enough or in sufficient contact with the stomach wall to mirror the entire organ. Second, at a given moment, the balloon may lie in the pyloric portion and fail to reproduce fundic waves, particularly if the algebraic sum of contraction wave preceded by dilatation fails to alter intragastric and therefore balloon pressure. Third, even if the balloon lies in the path of the wave the algebraic sum of all effects on pressure may be zero. Fourth, pyloric waves are more effective than fundic ones. Fifth, the ordinary stomach balloon usually lies in the fundic portion. To obtain a more comprehensive picture of the entire stomach in action which usually has two or more waves passing at the same time, two or three separate balloons could be used lying in different portions of the stomach. However, even this method is not entirely accurate. The electrical stresses summate in a manner different from the mechanical changes. It is obvious that under certain circumstances, the electrical stresses may nullify each other in the direction of the lead in use and result in no change or shift in the electrical record. Nevertheless, enough is shown

to give objective evidence of mechanical muscular activity associated with electrical changes

Study B Direct leads were placed on the abdomen to approximate the positions of pyloric and cardiac ends of the stomach. The stomach balloon was connected to the Frank capsule as in the preceding record (Figure 2)

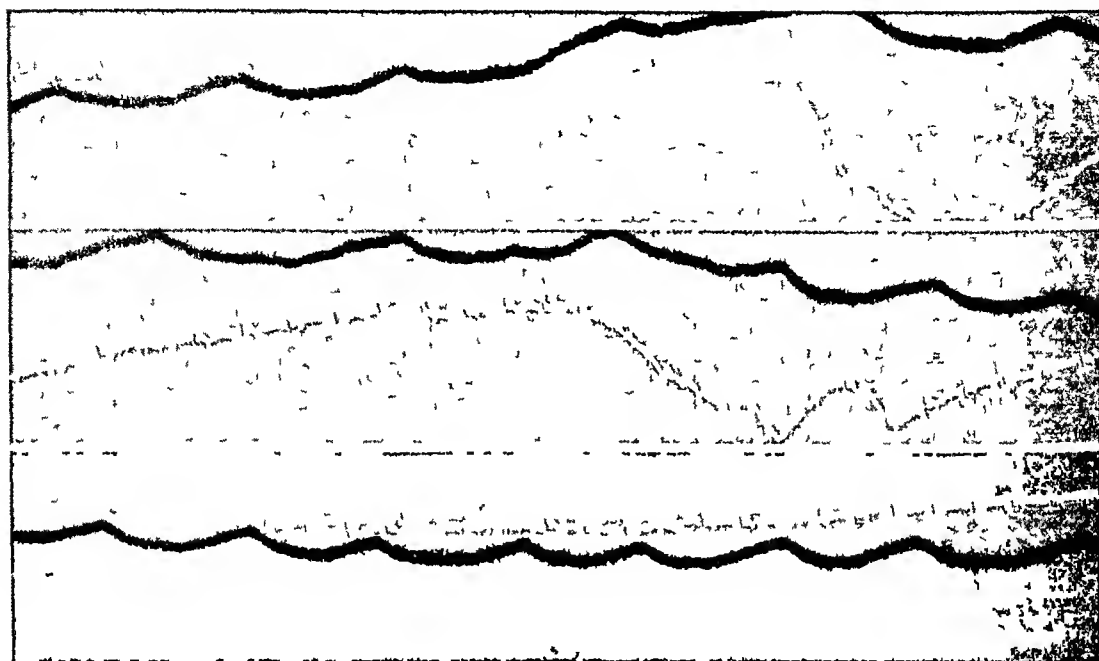


FIG 2 Simultaneous gastric electrogram by direct abdominal leads and mechanogram by balloon. Note marked excursions of electrical and mechanical tracing and lack of absolute parallelism

Comment By this method the electrical undulations were extremely marked. Polarity was such that the electrical and mechanical records sometimes moved in opposite directions as the contractions enhanced the mechanogram deviations. The record submitted minimizes the electrical excursions because the string repeatedly moved off the camera slot and had to be returned. At one point the measurement indicated a 30 millivolt change. To answer the question whether the marked excursions might be artefacts due to the position of the abdominal wall and the change in position of the electrodes which were forced up during the marked peristaltic bulgings, the patient was instructed to vigorously distend and contract his abdomen by deep respirations. These measures and deep palpation of the epigastrium produced no significant effect. Therefore, it seems that gastric peristalsis alone produces a marked electrical wave which can be picked up when direct abdominal leads are employed. Furthermore, it was noted that the closer the left lead, i.e., the cardiac, was placed to the right, i.e., the pyloric, the greater the electrical excursions.

Study C The typical Lead III was restored, but the mechanical deviation was recorded by fastening a tambour commonly employed to record the cardiac apex beat in the path of the peristaltic wave (a) left upper quadrant in the fundic region, (b) mid line and (c) in the region of the pylorus

Comment Although the observations correspond with those obtained by the preceding methods, namely, that electrical and mechanical deviations were demonstrated together, there was more difficulty because the nature of the peristaltic wave prevented accurate apposition of the tambour to the abdominal wall at all times

Intestinal hyperperistalsis was observed in a girl with congenital hypertrophic dilatation of the colon (Hirschsprung's disease)

CASE REPORT

R M., a female of six and one-half years, was admitted to the Sarah Morris Hospital, service of Dr Jesse R Gerstley, October 18, 1934, for an acute dysentery which had affected three other members of the family after a meal of canned meat, and was discharged recovered from dysentery, November 5, 1934. Interest in connection with the present study lay in the fact that constipation had been present since the child was 14 days old. At this time she had no bowel movement for five days. At present she requires an enema every two or three days without which there is no evacuation. There has been loss of sphincter control at intervals since infancy. These involuntary movements are sometimes loose and associated with simultaneous urination. Further, there is frequent involuntary urination when the bowels are unusually constipated. (It should be stated here that atony of the bladder is commonly associated with atony of the colon and is usually overlooked in the history and examination.) It was also volunteered that the child had never been quite well and that her extremities had remained poorly developed while her abdomen became large and protuberant.

Physical examination revealed a small undernourished girl with thin arms and legs and an unusually large abdomen, slightly toxic and feverish. Aside from the specific illness for which she was admitted, it was noted that a relatively long torso gave a peculiar appearance. There were large peristaltic waves passing from right to left across the abdomen and also down the left side of the abdomen from above, following the course of the colon. Tympanites was present, and the bladder was distended. An opaque enema revealed a localized segment of dilated distal colon. The enema filled the dilated loop and extended backward to fill a tremendously dilated colon throughout. After 24 hours practically the entire enema was still present within the colon.

Study D Lead III which was used in other portions of this report was employed for the electrical record. A tambour was placed on the abdomen connected for photographic registration of mechanical effects as described above. (Figure 3)

Comment The wide deviations of the band which again reproduces the mechanical record indicates the violence of the intestinal peristalsis. This is further evidenced by the tracing leaving the limits of the camera in several places. Equally conspicuous is the marked rise and fall in the electrocardiographic base line associated with the greatest activity of peri-

stalsis In the portion of the record here illustrated it is mere chance that the electrical and mechanical excursions are in the same direction because a wave in another segment of colon may be associated with an electrical wave in the opposite direction depending on the interference and direction of the interference of the electrical axis A review of results in a previous study

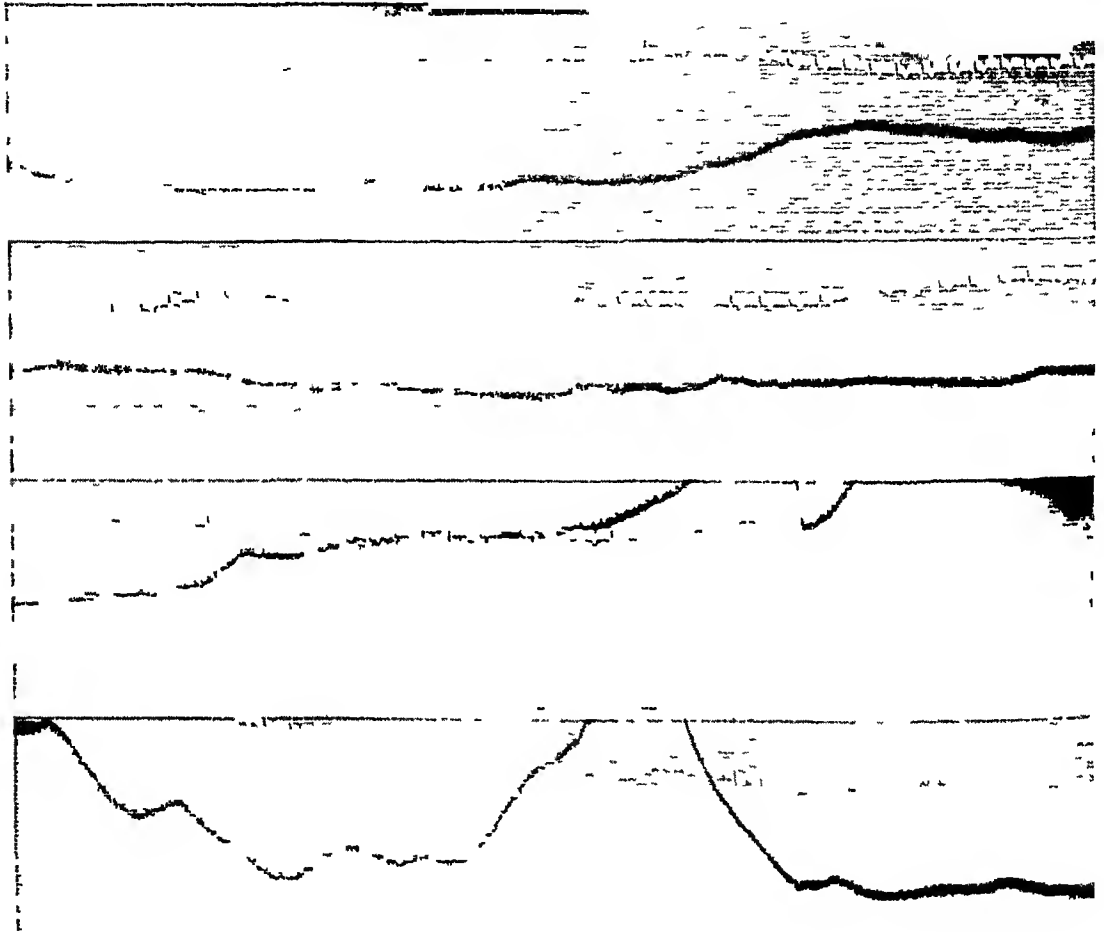


FIG 3 Simultaneous electrogram by Lead III and intestinal mechanogram by tambour
Note degree and direction of fluctuations

in intestinal hyperperistalsis in a two year old child with Hirschsprung's disease and in a 60 year old man with borborygmi will recall that there is no regularity in curves because the intestinal wave is a variable at any given moment in direction, intensity and location These variable factors must affect the electrocardiogram irregularly The waves in the present subject were of marked intensity, and the algebraic sum of the peristaltic effects, checked visually, is illustrated in the reproduction It is obvious that the tambour method is limited by the fact that it can only reproduce the mechanical changes of one small area, but it is useful in objectively denoting the mechanical effect of peristalsis and is an objective substitute for mere visual evidence

SUMMARY

1 Simultaneous mechanical and electrical registration of gastric hyperperistalsis is recorded for the first time in the intact human subject upon the electrocardiographic film

a The electrogastrogram and the mechanogastrogram resemble each other in form and contour because there is fixed polarity in gastric peristalsis

b The exact reflection of the electrical action current in gastric peristalsis cannot be mirrored by the balloon or tambour method because of the limitations of this method of reproducing the mechanical factor in contraction

i The algebraic total of contraction in electrical terms in its effect on the electrocardiogram is recorded

ii The algebraic total of stomach activity by changes in intragastric pressure or pressure within balloon or tambour is at best but crudely reproduced

2 Simultaneous electrical and mechanical registration of intestinal hyperperistalsis is recorded

3 This study accomplishes its purpose which was to confirm the author's previous observations by submitting objective evidence of simultaneous gastric and intestinal hyperperistalsis accompanying disturbances of the electrocardiogram coincident with visible peristalsis

4 An exact picture may be possible by simultaneous cinematographic roentgenographic reproduction of visible peristalsis using a double coated barium treated balloon and electrocardiographic records run on film at equal speeds

5 This study confirms the fact previously established that the movements of the base line of the electrocardiogram are the electrical evidence of hyperperistalsis and can properly be called hyperperistalt-electrograms

6 Indirect electrical leads are adequate and may serve a useful function in the study of peristalsis

I wish to acknowledge indebtedness to Dr Heinrich Necheles of the Department of Gastro-Intestinal Physiology for his suggestions and assistance and to Dr Louis N Katz, Director of Cardio-Vascular Research, for advice on methods of registration and for his valuable suggestions in the preparation of this report

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THE VALUE OF THE SEDIMENTATION TEST AS A DIAGNOSTIC AID *

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IN 1918, Fåhræus¹ called attention to the fact that there was an increase in the sedimentation rate of red blood cells in the citrated blood of pregnant women. This was immediately hailed as a new test for pregnancy. However, it was soon discarded, as it was found to be unreliable, until after the third month of pregnancy.

Fåhræus was not the first to make this interesting observation. Galen, as early as the year 200, pointed out that if blood were allowed to stand in a tube, a white line would form at the top of the blood. While he did not recognize this white line as coagulated plasma, he did regard it as pathological, and referred to the phenomenon as the "Crusta Phlogistica." In 1791, John Hunter noted that the erythrocytes of the blood settled more rapidly in inflammatory conditions than they did in normal blood. Further observations were made by Nasse in 1836, Davy in 1839, Muller in 1844, and Biernacki in 1894.²

The test was then forgotten until the work of Fåhræus. In 1920, Linzenmeier³ called attention to its usefulness in the diagnosis of pyosalpinx. Friedlander in 1924, Polak in 1926, and Baer and Reis, in the same year, called further attention to its use in gynecology and obstetrics, while Wehrbein, in 1928, stressed its importance in urology.

TECHNIC

Unfortunately, there are three different methods of performing this test, and each in turn has different modifications, made by various investigators. The first method is that of Fåhræus and Westergren. The underlying principle in this consists of measuring the distance through which the red blood cells fall in one hour, and the results are recorded in millimeters. The second is the Linzenmeier³ method, in which a record is made of the time in minutes necessary for cells to settle a given distance of 18 millimeters in a column of blood 50 millimeters high. The third is the graphic method of Cutler,⁴ in which the use of a graph is especially valuable, as it shows any sudden change in velocity.

Greisheimer⁵ and his associates have pointed out that the average sedimentation rate in one hour for "normal" subjects appears to be reasonably concordant for the three methods, despite the wide difference in the width of the tubes, the length of the fluid column, and the anti-coagulant concentration.

Wintrobe and Landsberg⁶ have emphasized the necessity of a standard test and pointed out many possible sources of error in performing the test.

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The most important are the following: The effect of the anti-coagulant, the influence of the bore and length of the tube, the influence of the inclination of the tube, the effect of the room temperature, the changes in the suspension stability of blood, as influenced by delay, in carrying out the test.

In our work, the Schiller modification of the Fåhræus-Westergren method was used. It has several advantages, the most important being that the technic is simple, the time required for observation is only one hour, the recording of only one reading is necessary, and the blood is obtained from the finger and not the vein.

A capillary tube 138 millimeters long and 1 millimeter in calibre is used. There are two marks on the tube, the first being 13 millimeters, and the second 63 millimeters from the tip. After preparing the patient's finger in the usual manner, and making a quick puncture, a 5 per cent solution of sodium citrate is drawn up to the first mark, and the patient's blood is immediately drawn to the second mark, great care being exercised to prevent the formation of air bubbles. The tube, which contains 0.4 c.c. of citrate and 1.6 c.c. of blood, is gently tilted 20 times to allow the solutions to mix. The tip of the tube is then plugged with a tiny piece of soap and carefully placed vertically in an especially constructed rack, which has clamps to hold the tube very firmly. After exactly one hour, the amount of clear fluid at the top of the tube is read and recorded in millimeters. The normal rate for males is 2 to 8 millimeters, the average being 4 millimeters, while the normal for females is 3 to 10 millimeters, with an average rate of 6 millimeters. The normal rates for infants, children and senile individuals, is slightly greater, while the same is true of menstruating women.

THEORY

Various factors influence the speed with which erythrocytes settle but, as yet, the exact mechanism of the sedimentation test is not known. Numerous explanations have been advanced. Fåhræus¹ believes that increased sedimentation is produced by an alteration in the electrical charge of the blood corpuscles, causing a loss of their repelling force, and thereby bringing about their agglutination and more rapid sedimentation. Reynier⁷ holds that a difference in surface tension of blood plasma is responsible for the phenomenon. Hunt⁸ states that whatever is responsible for the increased sedimentation is contained in the blood plasma, and that it is most likely an increase in the fibrinogen. According to Snappier,⁹ the two chief factors influencing the rate of the fall are the concentration of fibrinogen and serum globulin, with hydration or degree of anemia acting as subsidiary factors. Hoverson and Petersen¹⁰ regard the variations in the individual rates as dependent largely on environmental and meteorologic conditions. According to Gram,¹¹ the sedimentation rate depends on (a) the cell volume percentage, (b) the fibrin percentage in the plasma, and (c) the temperature. On the other hand, Bortree¹² states that the relative speed of sedimentation

of erythrocytes is dependent upon the colloidal chemistry of the blood and chiefly upon the fibrinogen-globulin ratio Koelsche¹³ thinks the rate of sedimentation is directly proportional to the content of fibrin in the plasma. He points out that the blood of an anemic patient has a rapid sedimentation rate, notwithstanding its normal content of fibrin. An increase in viscosity of the blood inhibits sedimentation. Rubin and Smith¹⁴ conclude that, in general, the lower the hemoglobin content of the blood, the more frequently is increased sedimentation obtained. They believe that the volume of red blood cells exerts an important influence on the sedimentation rate, under all conditions, and that possibly physiologic changes in sedimentation are also influenced, to a great extent, by the erythrocyte factor. Thus, the lower cell volume percentage found in women would explain the greater sedimentation reactions that they give in comparison to men. Among the various explanations of the varying rate of sedimentation of erythrocytes, Banyai and Anderson¹⁵ feel that the most plausible are (a) an increase in the fibrinogen content of the blood plasma and (b) changes in the number and size of the erythrocytes. Toxin production involves a breaking down of tissue proteins, and subsequently, the products of disintegrated tissue proteins will stimulate fibrinogen formation. As Cutler¹⁶ points out, there is constantly a process of tissue destruction, accompanied by a similar amount of tissue repair. Should the amount of tissue destruction pass beyond the normal, then the stability of the blood is seriously disturbed and the red blood cells settle out quickly from the plasma, the rapidity of the settling of the red blood cells being in direct proportion to the severity of the disease.

We believe the sedimentation rate depends on the presence of a foreign protein in the circulation. In pregnancy, this is the protein of fetal catabolism, in infection, it is the protein of bacteria, and in malignancy or coronary occlusion, it is the protein of necrotic tissue.

USES

As stated above, this test was first devised as a test for pregnancy. However, more recently, it has received recognition as a useful diagnostic adjunct in other branches of medicine. Westergren¹⁷ claims that it not only has diagnostic value, but also furnishes information as to prognosis, as well as indications for therapy.

Cutler¹⁸ presents the amazing statistics of 5,000 patients, on whom sedimentation tests were made. Of this entire group, there were only five patients on whom a normal rate was obtained, in the presence of active disease. Yates and Davidow¹⁹ made 6,000 determinations on 1,700 patients and found the accuracy of the sedimentation test to be 91.4 per cent.

In our own work, we performed 488 sedimentation tests on 395 patients. Of 283 determinations that should have given normal sedimentation rates, only 11 had rates that were over the normal limit. Of the remaining 205 determinations which were expected to be abnormally high, there was not one single case that gave a rate of less than 15 millimeters.

Gallagher²⁰ presented figures on 685 normal school boys and concluded that the test produced most valuable results. In his group there were many patients with mumps and the "common cold." These gave normal rates, showing how little the sedimentation rate is affected by minor infections, of short duration.

The sedimentation test has been used very extensively in the field of gynecology. Grodinsky² called attention to an increased rate in pyelitis, pyelonephritis, pyonephrosis and perinephric abscess. He found that ureteral colic, and other urological conditions, without associated infection, gave a normal rate, and emphasized the importance of this in the differential diagnosis of pain in the lower right quadrant. He further noted that acute appendicitis without rupture had a relatively low rate, while subacute and chronic appendicitis gave even a lower figure. Polak and Tollefson²¹ cite 1,660 readings on 650 gynecological patients. They concluded that rapid sedimentation indicated infection, when the readings in pregnancy and the puerperium had been excluded. In the presence of a high rate, these authors never operate on a patient, unless there be inflammatory process too active to permit conservative procedure. Furthermore, the test is used as an indicator by these investigators, as to the proper time to discharge the patient from the hospital. The individual is not released, until the rate returns to normal, excluding, of course, all other sources of infection. Polak and Tollefson use as their dictum, "The sedimentation test never lies." Ward²² used the test in 1,140 cases and reached the same conclusion. Friedlander,²³ after testing 1,500 patients, felt that the test was extremely valuable in determining the "safe period" for operation. Schattenberg²⁴ after 1,100 tests, Rubin,²⁵ Nicholson,²⁶ and Stimson²⁷ are all in accord in this respect.

Smith, Harper and Watson²⁸ in their report of 19 cases of acute salpingitis and 38 cases of acute appendicitis, came to the conclusion that the sedimentation test is of some value as a differential point between these two conditions. Nicholson²⁶ was of the same opinion.

Mathieu, Trotman and Haskins²⁹ performed 2,100 tests on 1,145 patients. Of these, 220 tests were on healthy women. They found that in abortions without infection, the sedimentation rate returned to normal, 15 days after curettage. They further noted that in eight cases of ruptured ectopic pregnancy, the sedimentation rate was increased, but in no case was it as high as in acute or subacute salpingitis. The difference, however, was not sufficient to regard this as a differential test between the two conditions. They found normal rates in 40 cases of trichomonas vaginalis vaginitis, 13 cases of Frohlich's syndrome, and 80 cases of cystocele, rectocele, retroversion and prolapse of the uterus, but the rate was definitely elevated in 23 cases of infection of Skene's or Bartholin's glands.

Lesser and Goldberger³⁰ reported 2,000 cases of all conditions with 3,000 readings. They felt that it was even possible to differentiate acute appendicitis from acute rheumatic fever with abdominal symptoms, by

means of this test. The latter had a very high, while the former had an absolutely normal reading. They included 75 cases of acute appendicitis made up of catarrhal, gangrenous and suppurative, and observed that uniformly the sedimentation rate was normal, regardless of the pathologic lesion noted. On the other hand, all other types of acute surgical conditions in the abdomen, including ruptured appendix, gave an elevated reading.

Rubin²⁵ concluded that in surgery, the sedimentation rate is a more reliable indication of the condition of the patient than the temperature chart. Nystrom and Geisheimer,³¹ in reporting 57 gynecological cases, and Smith, Harper and Watson²⁸ feel that the sedimentation test gives more valuable information than the temperature chart or the white blood count.

On the other hand, Simmich,³² after an observation of 150 gynecological patients, of whom 132 had laparotomies, stated that the sedimentation rate was not a reliable guide in the determination of the safe operative time, and Williams³³ concluded after his study that the temperature curve and the study of the leukocytes remain as more stable indices for diagnosis and prognosis. Peterman and Seeger,³⁴ in reporting 150 cases in children, were of the same opinion.

From our studies, we are inclined to disagree with the views of this latter group. We observed 73 cases, which were normal in every respect and which had a normal sedimentation time but in whom the white blood count was over 10,000 in each case. Of these 73 cases, 19 had white counts of over 13,000 and in seven of these, the white blood count was over 16,000.

In 70 of these cases, the differential count was normal. One of these cases was especially interesting. The patient, a man of 42 years of age, had evidence of myocardial damage. He continued to have fever and leukocytosis for several months, during which time the sedimentation rate remained absolutely normal. Very careful investigation revealed no evidence of infection, and after a time the fever and leukocytosis disappeared (Table 1).

TABLE I

The laboratory records of a patient showing fever and leukocytosis together with a normal sedimentation rate

Date	Hb	R B C	Sed Rate	W B C	Diff	Temp
3/11/35	90	4,560,000	8	12,300	Normal	99.4
3/20/35	88	4,620,000	7	11,900	Normal	99.1
4/8/35	88	4,640,000	8	10,150	Normal	99.0
4/24/35	90	4,720,000	6	12,900	Normal	99.2
5/5/35	87	4,670,000	8	17,400	Normal	98.4
5/20/35	89	4,700,000	8	16,200	Normal	99.0
6/5/35	86	4,680,000	7	11,950	Normal	99.1
6/24/35	88	4,800,000	8	10,250	Normal	99.1
7/1/35	89	4,840,000	6	11,200	Normal	99.2
8/13/35	90	4,750,000	3	8,600	Normal	99.0
9/3/35	87	4,680,000	5	13,700	Normal	98.4
9/13/35	89	4,320,000	8	17,200	Normal	99.0

Malignant growths, if extensive, usually give a high sedimentation rate,

while a slow growing benign tumor without necrosis gives a normal rate. However, after irradiation of any tumor, the rate of sedimentation increases, probably due to decomposition of the tumor, with a resultant increased amount of foreign protein in the blood. According to Schiller,³⁵ if a malignant growth be removed operatively, the sedimentation rate should return to normal within six weeks, if complete removal was obtained. If the rate returns to normal, and remains normal at least six months, one may give a guardedly favorable prognosis. If the rate becomes abnormal within this time, it is suggestive of local recurrence of the growth or metastasis. In one of our cases, the patient, a woman of 62, had what appeared to be a typical fibroid, about the size of a grape fruit. The hemoglobin was 85 per cent, r b c 4,730,000, w b c 6,750, and the differential count was normal. The sedimentation rate, however, instead of being the normal as in a simple fibroid, was 32. The uterus when removed appeared grossly to be a fibroid, but on closer microscopical examination, malignant degeneration was found to have occurred at the central part of the tumor. Two months after the operation, the sedimentation rate was 8. There were seven other cases of malignancy in our group, with 19 determinations, all of which were over 28 millimeters. Four of these were carcinoma of the stomach, and in each the hemoglobin was over 65 per cent. It is interesting to note that, on the other hand, there were 11 cases of definite duodenal ulcers with a total of 28 determinations, and in not one did the readings go over 6 millimeters. Four of the cases had hemoglobin lower than 65 per cent.

One of the greatest uses for this test is in determining the degree of certain infections. If the infection be in the active state, the rate will be high, while if the infection be in the arrested state or state of repair, the rate will be low. It has been especially useful in infectious arthritis and tuberculosis. Oppel, Meyers and Keefer³⁶ studied 107 patients with various forms of arthritis and 103 with a miscellany of diseases, as a control group. They found a great variation in the sedimentation rate in different types of arthritis, the most rapid rate being in acute rheumatic fever, rheumatoid and gonorrheal arthritis. In our series, there were 23 readings made on nine patients with acute arthritis. In each the rate was elevated, ranging from 26 millimeters to 48 millimeters. An interesting observation is the uniformity of this test over a long period of time, as compared with the marked variability of the white blood count. (Table 2)

TABLE II
A case of acute arthritis illustrating the relative constancy of the sedimentation rate

Date	Hb	R B C	Sed	W B C	Polys
10/15/34	85	4,340,000	38	10,600	74%
11 15/34	80	4,130,000	33	13,350	76%
12/14/34	80	4,000,000	32	12,300	73%
1/15/35	82	4,730,000	36	10,000	74%
2/23/35	82	4,600,000	34	12,400	71%
3/23/35	86	4,920,000	36	7,600	73%
4/18/35	80	4,250,000	35	10,850	70%

Furthermore, as the patient improves, there is a tendency for the sedimentation rate to decrease (Table 3)

TABLE III

Case illustrating parallelism of clinical improvement and decrease of sedimentation rate

Date	Hb	R B C	Sed	W B C	Differential	General Condition
7/24/35	91	4,480,000	39	9,700	Normal	Bed-ridden Painful swollen feet
9/ 8/35	90	4,670,000	24	7,200	Normal	Bed-ridden Feet not so red
9/25/35	90	4,600,000	8	9,950	Normal	Ambulatory Feet not so red or painful
10/10/35	92	4,650,000	5	10,100	Normal	Feet much better Condition greatly im- proved

This is not only true in arthritis, but also in other infections Table 4 represents the findings in a patient of 14, with acute endocarditis, who showed simultaneous improvement in his clinical condition and in the sedimentation rate

TABLE IV

Case of rheumatic carditis showing clinical improvement and decreasing sedimentation rate

Date	Hb	R B C	Sed	W B C	Differential	General Condition
8/13/35	83	4,430,000	36	7,300	Normal	Bed-ridden, dyspnea, pain
9/ 3/35	85	4,460,000	25	6,000	Normal	Bed-ridden Slower pulse
9/16/35	82	4,310,000	14	11,650	Normal	Bed Less dyspnea
10/ 1/35	83	4,300,000	7	6,850	Normal	Sitting up No fever or pain
10/15/35	86	4,510,000	5	10,300	Normal	Ambulatory, much im- proved

In tuberculosis infections the sedimentation rate is high in the presence of activity and normal in the arrested stage The value of this test in tuberculosis has been widely recognized, especially in the European clinics In certain Austrian tuberculosis sanatoria, a sedimentation test is made routinely three times a week on each patient The usefulness of the test in this field is emphasized by Grafe³⁷ who reported 500 cases, Rubin,³⁸ Van Antwerp,³⁹ Cutler and Cohen,⁴⁰ Banyai and Anderson,⁴¹ Ringer⁴¹ and others Cutler and Cohen believe it to be 94 per cent accurate in tuberculosis They point out that a higher reading is obtained if the patient is unduly excited Banyai and Anderson, in 2,000 cases, found a normal sedimentation time in 128 cases with signs of activity, an error of 7.35 per cent They feel that the test's greatest value is in its use as an objective measure of the course of the disease It serves as a sensitive indicator of complications or the development of new foci, and as a criterion of results obtained

by a regimen or a specific treatment. New foci in lung tissue are sometimes not suspected, and complications like intestinal or renal tuberculosis are often not detected until an increase in the sedimentation rate has led to a careful search. It offers an approximate gauge of the extent of improvement when physical or roentgen examination may be of little value. Ringer pointed out that a rise in the rate in a tuberculous patient may precede hemoptysis. His two years experience with the test has convinced him that the test is one of real value. It reinforces physical, radiological and symptomatic evidence, and frequently presages oncoming trouble. He emphasized the fact that no tuberculous patient should be discharged until the sedimentation rate is normal. In our small series, we had six arrested cases of tuberculosis, none of which had a sedimentation time of over 7 millimeters, and one active case with a rate of 39.

In addition to these, there are other uses for this test as mentioned by Sivinsky,⁴² Tulipan and Director. Recently attention has been drawn to its usefulness in cases of coronary occlusion. In this condition the rate becomes elevated a few hours after the onset of the attack. The increase is probably due to the absorption of necrotic tissue from the produced myocardial infarct. After reaching its peak, the rate gradually diminishes. The duration of this period of elevated rate may serve as a guide in determining how long the patient should be kept at rest. It may therefore prove useful not only as a diagnostic measure, but also as a measure of the healing of the infarct. (Table 5)

TABLE V
The sedimentation rate following coronary thrombosis

Patient	Sed Rate prior to Attack	1st Wk of Attack	3rd Wk of Attack	4th Wk of Attack	5th Wk of Attack	6th Wk of Attack	12 Wks after Attack
E W E	6	46	35	25	10	7	5
C W G	7	45	42	20	7	5	4
T H	—	40	32	24	16	8	—
H L M	4	58	44	30	20	7	6
C S	—	45	36	21	15	8	—
A G	—	48	—	—	—	—	—

SUMMARY AND CONCLUSIONS

1 The sedimentation test is a relatively simple laboratory procedure which is now soundly established as a valuable addition to our diagnostic armamentarium.

2 The sedimentation test is not a specific diagnostic test for any one condition, but the presence or absence of an increased sedimentation rate may have great value in differential diagnosis.

3 The comparison of repeated sedimentation tests is particularly useful in estimating the progress of disease. The test is now widely employed

in this manner in gynecological diseases, in tuberculosis, in rheumatic infections, in malignant growths and recently in coronary occlusion

4 The results obtained in 488 sedimentation tests on 395 patients were found confirmatory of the reliability of the test. Charts furnishing examples of the utility of the test are included. The results obtained with the test in six cases of coronary occlusion are tabulated

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CLINICAL EXPERIENCES WITH REDUCED DOSES OF THEVETIN ORALLY ADMINISTERED ~

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CLINICAL studies of the action of thevetin^{1,2} have amply confirmed the pharmacologic results of Chen and Chen^{3,4} and established its reliable digitalis-like effect in man. The pulse is slowed, evidences of decompensation are alleviated, diuresis ensues and characteristic electrocardiographic changes occur when thevetin is given either by the oral or the parenteral route. Its untoward by-effects also parallel those of digitalis with a singular deviation in the gastrointestinal action. Here intestinal effects (cramps and diarrhea) in the main replace the common gastric upsets (anorexia, nausea and vomiting) incident to digitalis intoxication.

The galenical preparations of the defatted be-still nuts, which are the source of the glucoside, thevetin, gave practically constant evidences of gastrointestinal irritation¹. Indeed, this action was so serious as to preclude their further clinical trial. On the other hand the glucoside, thevetin, parenterally or orally administered, proved a distinct improvement over the galenical products in this respect^{1,2}. Even with thevetin, however, 16 of 40 patients with cardiac decompensation showed some gastrointestinal effects². Of this group 11 patients after a period of rest were able to resume the use of the drug without a recurrence of abdominal symptoms. The failure of concurrently administered belladonna to control the cramps and diarrhea caused by thevetin argues against Chopra and Mukerjee's suggestion that these phenomena are due to peripheral vagal action⁵. Furthermore, atropinized intestinal strips from the rabbit show vigorous contraction upon the application of thevetin².

A re-survey of the situation² evolved certain illuminating circumstances. The minimal emetic dose of thevetin is equivalent to 35 per cent of the cat unit as compared with 50 per cent for ouabain. Intestinal strips of rabbits are stimulated by minimal concentrations of thevetin and ouabain in the ratio of $3\frac{1}{3}$: 1 as compared with the ratio of cat unit values of 7 : 1. In other words one may expect gastric and intestinal effects much more promptly in relation to the cat unit with thevetin than with ouabain. Clearly, too, the intestinal action of thevetin may be expected to precede its effect on gastric function.

On the other hand a maximal bradycardia is induced with 30 per cent of the cat unit of thevetin as compared with 58 per cent for ouabain. Accordingly it seemed reasonable to anticipate an optimal clinical advantage with one half the cat unit dosage of thevetin as compared with ouabain. Since

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TABLE I

No	Age	Sex	Wt	Prior Digitals	Type Heart Dis	Thevetin Dosage	Interval Days	Initial Effect				Further Thevetin	Subsequent Effect				Comment	Symbolic Value of Thevetin Therapy
								Circulatory		Gastric	Intestinal		Circulatory		Gastric	Intestinal		
					Subjective			Objective	Subjective				Objective	Subjective				
1	49	M	186	Tr. M. XV t i d 12/28/35 to 1/9/36 Maintenance M V t i d	Rheumatic, Grade III	M X t i d	3	0	0	Nausea, Vomiting	Diarrhea	M V t i d (3 days)	0	0	Involuntary diarrhea	After 3 days of thevetin pulmonary infarction occurred. Expired 11th hospital day. P M Mural thrombosis left auricular appendage. Pulmonary infarcts on left with CPC lungs liver and spleen	-	
2	56	M	210	Tr. M. XV t i d. Indefinite M XV t i d on 1st day of admission	Hypertensive, Grade III	M XV t i d	5	Improved less dyspnea	0	0	Vagal effect, Diuresis, Edema reduced	0	Improved	Maintained vagal effect	Anorexia 3 days, better for 5 days	Pain left abdomen. Tendency to loose bowels (1 day) No diarrhea	Improvement marked with diuresis. Thevetin begun on 7th hosp day. Nausea followed. Thevetin discontinued after 3 days. Nausea disappeared 2 days later. Signed his own release on 22nd hospital day	+
3	62	M	142	0	Arteriosclerotic, Grade IIB	M X t i d	6	0	0	0	Vagal effect	M V t i d 1 day	0	Pulse maintained at slower rate	0	Patient severe asthmatic, which was primary condition	+	
4	50	F	106	0	Thyrototoxic, Grade IIB	M XV t i d	3	0	0	0	Vagal effect marked	M XV t i d 3 days M V t i d 6 days M XV t i d 1 days	0	Pulse was maintained at a slower rate	Nausea	Cramps, Diarrhea	This patient had thyroidectomy. While thevetin slowed the pulse rate it caused diarrhea nausea and cramps. Finally was discontinued and patient placed on digitals	- +
5	45	M	167	0	Hypertensive Grade III	M V t i d 1 day, M X t i d	8	Improved	0	0	Early vagal effect Diuresis Decreased cyanosis	M V t i d 1 day	Continued improvement	0	0	Patient also received theophylline gr iss t i d and ammon chloride. Later theococ gr X given t i d for 3 days. Early vagal effect not maintained proportionally to general advantage	+	

* Symbolic Value of Thevetin Therapy

Circulatory advantage marked +

Pronounced gastrointestinal effects and less marked circulatory response, ±

Predominant gastrointestinal effects and minor circulatory response -

TABLE I—Continued

No	Age	Sex	Wt	Prior Diarrhea	Type Heart Dis	Thevetin Dose	Interval Days	Initial Effect				Further Thevetin	Subsequent Effect				Comment	Symbolic Value of Thevetin Therapy*
								Circulatory		Gastric	Intestinal		Circulatory		Gastric	Intestinal		
								Subjective	Objective				Subjective	Objective				
6	61	M	165	M X t i d 5 wks Digalen gr us t i d 1 week	Arteriosclerotic, Grade III	M XV t i d	3	Improved	Diuresis Vagal effect marked	0	0	M XV t i d 1 day, M V t i d 2 days, M X t i d 2 days, M V t i d 5 days	Cyanosis Dyspnea	Diuresis (slight)	Nausea Anorexia	Diarrhea no cramps	In view of anorexia and loose stools thevetin was discontinued although vaginal effect was obvious. Placed on diuretic. Symptoms of nausea, anorexia, diarrhea persisted. Patient expired 48 days following discontinuance of thevetin	- +
7	72	M	177	0	Hypertensive Grade III	M X t i d	8	Less dyspnea, Improved	Decrease in pulmo- nary con- gestion Vagal effect marked	0	0	M V t i d 4 days M VIII t i d for 11 days	Improved	Pulse maintained at slower rate	Slight nausea Anorexia	0	Developed a patch of bronchopneumonia on 35th hospital day. Recovery uneventful	+
8	71	M	169	0	Arteriosclerotic, Grade III (Lymphocytic leukemia)	M X t i d	0	Improved	Vagal effect marked	0	0	M X t i d 7 days V t i d 22 days	Improved	Pulse maintained at slower level	0	Diarrhea	Picture complicated by a chronic lymphatic leukemia for which he was given deep roentgen ray therapy. Diarrhea controlled upon lowering dosage of thevetin	+
9	51	M	7	Tr M XV t i d for 1 month	Thyrototoxic Grade III	M XV t i d	8	Improved	Pulse slowed, marked vagal action	0	0	M V t i d 15 days M VIII t i d for 7 days	Improved	Pulse maintained at slower level	0	0	Auricular flutter with varying degrees of block began 8 days after use of thevetin. Thyroidectomy done following which no digitalis or thevetin was given. Signs of decompensation returned. Patient was placed on digitalis by reason of change in service	+
10	55	M	7	0	Thyrototoxic, Grade III	M XV t i d	6	Improved	Pulse slowed diuresis Edema decreased	0	0	M V t i d 28 days	Improved	Dyspnea persisted	0	0	Thevetin used following which there were cramps and diarrhea. Thevetin stopped and cramps disappeared. On continued use of thevetin pt became constipated. It expired 5 days following removal of thyroid gland ? Pulm embolism	+

TABLE I—Continued

No	Age	Sex	Wt	Prior Digitalis	Type Heart Dis	Thevetin Dosage	Inter val Days	Initial Effect			Further Thevetin	Subsequent Effect			Comment	Symbolic Value of Thevetin Therapy
					Functional Cap			Circulatory	Gastric	Intestinal		Circulatory	Gastric	Intestinal		
								Subjective	Objective			Subjective	Objective			
11	54	M	222	0	Arteriosclerotic, Grade IIB	M XV t i d	4	0	0	Cramps Diarrhea	0	0	0	0	After 4 days of thevetin cramps and diarrhea developed. Placed on Tr digitalis M XXX t i d Suddenly expired 2 days later (Pulm thrombosis)	—
12	74	M	136	Tr Dig 1 month Amount ?	Arteriosclerotic, Grade IIB	M V t i d	6	Improved	Continued vagal effect	0	0	0	0	0	Patient had been fairly well digitalized before admission. He was kept on a maintenance dosage of thevetin	+
13	41	M	168	On digitalis 4 months Amt ?	Rheumatic Grade IIB	M XV t i d	5	Improved	Vagal effect	0	0	Improved	Pulse maintained at slower level	0	On thevetin M V patient complained of constipation. Progressive improvement. Change to digitalis made 'heart pound	+
14	90	M	180	Tr Dig M X t i d for 2 days	Arteriosclerotic, Grade IIB	M X t i d 3d M XV t i d 2 days	5	0	Vagal effect	0	0	Improved	Pulse maintained at slower level	0	Thevetin discontinued after diarrhea appeared. Def into vagal effect. Continued to improve after thevetin was discontinued	+
15	77	M	140	0	Arteriosclerotic, Grade III	M XV Q I D 4d M X t i d 10 days	14	Improved Less dyspnea	Vagal effect marked Diuresis Edema decreased	0	0	Improved	Pulse was maintained at slower level	0	Patient given a course of Thevetin gr X t i d just prior to marked diuresis. Edema disappeared. Dyspnea less marked	+
16	28	M	?	0	Rheumatic, Grade III	M XV t i d	5	Improved	Moderate vagal effect	0	0	Dyspnea Cyanosis	Cheyne-Stokes respiration	0	Picture complicated by chronic alcoholism and thyrotoxicosis. Pt expired with broncho pneumonia	—
17	49	M	?	0	Hypertensive, Grade III	M XV t i d	5	Improved	Vagal effect	0	0	Improved	Pulse at slower level	0	Circulatory balance was restored. Improvement was progressive and not attended by any complication	+
18	63	M	?	0	Arteriosclerotic Grade III	M X t i d	10	Improved Dyspnea less	Vagal effect Diuresis Decrease cyanosis	0	0	Improved	Pulse maintained at slower level	0	Picture complicated by Laennec's cirrhosis. Patient also given diuretics, ammonium chloride gr XXX t i d Abdominal paracentesis done	+

TABLE I—Continued

TABLE I—Continued

No	Age	Sex	Wt	Prior Digitalis	Type Heart Dis	Thevetin Dosage	Interval Days	Initial Effect					Further Thevetin	Subsequent Effect				Comment	Symbolic Value of Thevetin Therapy *			
								Functional Cap	Circulatory		Gastro	Intestinal		Circulatory		Gastric	Intestinal					
									Subjective	Objective				Subjective	Objective							
10	66	M	186	0	Arteriosclerotic, Grade III	M XV t i d	7		Improved Less dyspnea	Vagal effect marked Edema decreased	0	0	M V t i d 20 days	Improved	Pulse maintained at slower level Better water balance	0	0	Improvement in circulation was continuous and maintained	+			
20	42	F	91	Tr Digitalis M X t i d 16 days	Hypertensive, Grade III	M X t i d	3		0	Moderate vagal effect	Nausea	Diarrhea	M V t i d after 12 days	0	0	0	0	Patient was started on Tr Digitalis. Because condition did not improve changed to thevetin. Edema and congestion at bases persisted as well as gallop rhythm. Patient expired	-			
21	78	M	123	?	Arteriosclerotic, Grade IIB-III (Lymphocytic leukemia)	M V t i d 1 day, M XV t i d	4		Improved	Vagal effect Diuresis	0	0	M V t i d 15 days	Improved	Pulse maintained at slower level	0	0	Patient received eight 25 r units deep roentgen-ray therapy for leukemia	+			
22	59	M	180	Quinidine intermittently for 3 years	Arteriosclerotic, Grade III	M XV t i d	17		Improved	Vagal effect	0	0	0	Improved	Pulse maintained at slower level	0	0	This patient had an auricular fibrillation which had been treated with quinidine (amount not known) for 3 years. Precordial pain was fairly severe. Precordial pain was relieved for 1 week before discharge	+			
23	68	M	210	Digitalis Amount ?	Arteriosclerotic, Grade III	M X t i d	2		Improved	Vagal effect Diuresis	0	0	M V t i d 3 days	Improved	Continued vagal effect	0	0	Patient had been digitalized in Jan 1936, 4 months before present admission. Theophylline given with thevetin	+			
24	66	M	172	Digitalis ? Tr Dig M XV t i d, first day	Hypertensive, Grade III	M X t i d 1 day M V t i d	26		Improved Less dyspnea and orthopnea	Vagal effect diuresis Edema decreased	0	0	0	Improved	Continued vagal effect	0	0	Improvement in circulatory condition was progressive. Ammonium chloride and Mercupurin used with resulting profound diuresis. Abdominal and thoracic paracenteses done	+			
25	68	M	102	0	Hypertensive Grade III	M X t i d	8		Improved Less dyspnea	Vagal effect Edema decreased	0	0	M V t i d 8 days	Improved	Pulse maintained at slower level	0	0	Advantage maintained	+			

the earlier results indicated the appearance of a digitalis-like action from thevetin before theoretical tolerance on the body weight basis, such a readjustment of dosage seemed justified. At the same time the suggested reduced doses of 1 cat unit, three times a day, with a maintenance dose of 1/3 cat unit, three times a day, (as a maximum), offered the further prospect of an evaluation of the possible effect of such a reduction of dosage upon the incidence of untoward gastrointestinal symptoms.

A group of 25 patients with cardiac decompensation was subjected to this revised program of reduced thevetin dosage. In table 1 are listed their several diagnoses and the pertinent clinical data, particularly relating to therapy, and the results therefrom.

Turning to the results of treatment, under "Symbolic Value of Thevetin Therapy," there will be found a rough assessment of therapeutic response.

TABLE II
Initial Effect of Thevetin

	CLINICAL OBSERVATIONS	Total Cases	CASE NUMBERS
CIRCULATORY ADVANTAGE	Subjective, only	0	
	Objective, only	3	3, 4, 14
	Both, combined	19	2, 5, 6, 7, 8, 9, 10, 12, 13, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25
ADVERSE ACTION	Gastric symptoms, only (anorexia, nausea, vomiting)	0	
	Intestinal symptoms, only (cramps, diarrhea)	1	11
	Both gastric and intestinal symptoms	2	1, 20

Obviously 18 patients responded favorably to the alcohol solution of thevetin given by mouth and in one further patient (case 14) there was a good result with but slight diarrhea. In two patients (cases 4 and 6) the circulatory advantage did not compensate for the adverse gastrointestinal symptoms. Finally in three patients (cases 1, 11 and 20) the severity of the gastrointestinal disturbance seriously outweighed the action upon the circulation. While case 16 escaped gastrointestinal disturbances, there was no maintained circulatory advantage.

To throw further light on the problem of the balance between therapeutic advantages and the toxic drawbacks in the use of thevetin it was thought important to analyze the clinical data in this group of patients from the standpoint of the initial effect of the drug. This analysis is presented in table 2. At a glance it will be seen that in only three patients (cases 1, 11 and 20) did the toxic manifestations anticipate the therapeutic action of

the drug Interesting though this circumstance may be, it loses some of its significance when the necessity for a protracted action in this group of patients is called to mind Hence a summary of the ultimate effects of thevetin therapy is shown in table 3

It will be seen from this table that 19 of the 25 patients experienced a desired circulatory response from the oral use of reduced doses of thevetin and that two patients (cases 4 and 6) were assessed as doubtfully improved In the remaining four (cases 1, 11, 16 and 20) no appreciable advantage from the use of the drug was observed These results are comparable with those obtained when the routine of the Eggleston tolerance dosage was conformed to in the use of thevetin² More interesting is the analysis of the adverse reactions under the reduced scale of dosage Here it appears that 18 of the 25 patients were free from untoward symptoms and seven experi-

TABLE III
Summary of Ultimate Effects of Thevetin from Table I

	CLINICAL OBSERVATIONS	TOTAL	CASE NUMBERS
CIRCULATORY CONDITION	Improvement	19	2, 3, 5, 7, 8, 9, 10, 12, 13, 14, 15, 17, 18, 19, 21, 22, 23, 24, 25
	Doubtful improvement	2	4, 6
	No response	4	1, 11, 16, 20
UNTOWARD SYMPTOMS	Symptoms absent or negligible	18	2, 3, 5, 7, 9, 10, 12, 13, 15, 16, 17, 18, 19, 21, 22, 23, 24, 25
	Gastric symptoms, only (anorexia, nausea, vomiting)	0	
	Intestinal symptoms, only (cramps, diarrhea)	3	8, 11, 14
	Both gastric and intestinal symptoms	4	1, 4, 6, 20

enced either intestinal distress or intestinal and gastric disturbances In two patients (cases 8 and 20) diarrhea was controlled upon lowering the dosage of thevetin In a third (case 14) the circulatory advantage was maintained, but the glucoside was eventually discontinued upon the occurrence of a slight diarrhea (without recourse to the simple expedient of lessening the dose) Obviously then in only four instances (cases 1, 4, 6 and 11) may thevetin be charged with adverse gastrointestinal effects of such degree as to preclude its continued use and in each instance it will be observed that cramps accompanied the diarrhea It has been our experience with larger, as well as with reduced doses of thevetin that a mild diarrhea constitutes no sound objection to the continuance of the drug Indeed, there may be some advantage through the reduced physical effort of defeca-

tion Moderate to severe diarrhea and cramps, however, constitute as serious handicaps as do nausea and vomiting

When compared with the adverse results of thevetin therapy under an Eggleston regimen of dosage by body weight,² there is a distinct advantage in favor of the reduced doses Twenty-four of the earlier group of 40 patients (60 per cent) were free from symptoms as compared with 18 of 25 patients (72 per cent), in the present group Obviously the reverse of the picture is true, namely a higher incidence of gastrointestinal symptoms on the larger doses of thevetin than with schedule of reduced doses (40 per cent against 28 per cent) Apparently there is an individual idiosyncrasy to thevetin particularly in the occasion of intestinal cramps and this circumstance determined a small group in this series of patients, as well as the earlier groups, to whom thevetin was denied for this reason alone

The therapeutic-toxic ratio of digitalis-like drugs is so important that a search of the literature was made for studies of this type upon digitalis itself Generalities were found to prevail, but Bastedo⁶ reported a 35 per cent incidence of toxic symptoms among 90 patients receiving digitalis in Bellevue Hospital Whereupon Shanahan⁷ undertook an analysis of the matter from the materials in the records of the Wisconsin General Hospital A careful selection of materials was made to exclude those with prior digitalis therapy, inadequate control observations or other confusing factors Among a group of 65 patients with cardiac decompensation thus culled from a large series, he found that 37 per cent showed some evidence of digitalis intoxication at one time or other Furthermore 28 per cent of these 65 patients developed symptoms of the toxic action of digitalis before any circulatory advantage was attained Finally 22 per cent of the group showed such serious reactions to digitalis as to preclude its continuance

These figures are not quoted in extenuation of the untoward results from thevetin therapy Apparently a reduction of the dosage of this glucoside by mouth commensurate with its superior vagal effect has induced a lessening of the gastrointestinal action Nevertheless cramps and diarrhea do occur in an appreciable percentage of cases even under reduced doses In some of these, the adverse effects do not outweigh the circulatory advantage incident to the use of thevetin In others, the toxic symptoms preclude further use of the drug On the other hand in cardiac cases that do not tolerate digitalis well thevetin may offer the boon of a further reliable cardiac glucoside Moreover as has been reported earlier¹ thevetin possesses distinct advantages as a drug for emergency use by intravenous injection

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THE DIAGNOSIS AND TREATMENT OF HYPER-INSULINISM *

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THE recently recognized disease entity, hyperinsulinism, is being diagnosed with increasing frequency. Cases have been reported in practically every country in the world in which medical journals are published. It is interesting to observe the influence of American medical literature on clinical practices in foreign countries, and it is pleasing to note that, in nearly all the articles on hyperinsulinism and spontaneous hypoglycemia in foreign journals, the authors have been generous in their references to contributions on the subject by American physicians.

Among the many foreign clinicians who have reported cases of hyperinsulinism, or spontaneous hypoglycemia, or have published articles on the subject, may be mentioned Cammidge (1924 and 1930), Cameron (1930), Wauchope (1933), Cairns and Tanner (1933), of England, Moore, O'Farrell and Malley (1931), of Ireland, Sippe and Bostock (1933), of Australia, Posel (1933), of South Africa, Gougerot and Peyre (1925), Sendrail and Planques (1927), Laroche, Lelourdy and Bussiere (1928) and Sigwald (1932), of France, Krause (1930), Roth (1930), Wilder, Josef (1930) and Rosenberg (1932), of Germany, Bakser (1933), of Poland, Federoff (1931), of Russia, Stenstrom (1926), Sjogren and Tillgren (1927), Hagedorn (1932), Ehrstrom (1932), of Scandinavia, Massa (1929), Reale (1929), Lami (1930), Cimmino (1931), and Tarsitano (1931), of Italy, Zubirian (1929), of Mexico, and Valenzuela (1931), of Chile.

Hyperinsulinism Consciousness "Hyperinsulinism takes another syndrome from the waste basket of neuroses" is the syllogistic statement of Evans and McDonough, of LaCrosse, Wisconsin, who found and relieved six cases in six months' private practice after they became "hyperinsulinism conscious."

Powell, a general practitioner of West Monroe, Louisiana, found 25 cases of hyperinsulinism in two years after he recognized his first case. He concludes "Ample case reports are now in the literature to show that hyperinsulinism causes symptoms varying from drowsiness to narcolepsy, from vertigo to epilepsy, and from mental deficiency to mental degeneracy. Unfortunately all the cases are not in the literature—they are to be found in every doctor's clientele and, sad to relate, are most probably untreated."

Wilder, Allen, and Robertson, in 1927 made autopsy studies of an inoperable case of hyperinsulinism due to an islet cell carcinoma, and proved the pathological basis for the condition. Since then Wilder, Allen, Judd,

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Rowntree, Ryneerson and their associates have reported a number of cases, most of which have been operated upon. Wilder called attention to the erroneous diagnoses as applied to hyperinsulinism, including "nerves, neuasthenia and hysteria." He adds "Hypoinsulinism and hyperinsulinism are in fact clinical antitheses the latter is of as serious significance as the former, and the practitioner of today must be as familiar with one as with the other."

Marsh, of Madison, Wisconsin, who reported eight cases of mild hyperinsulinism in 1931, regards the condition as of frequent occurrence. Tedstrom, of Santa Ana, California, reported four cases and analyzed the literature on 64 other cases in 1933. In 1935 he states that he has had about 100 cases of hypoglycemia, most of which are due to hyperinsulinism.

It is not an accident that Carr, Parker, Larrimore, Graham, Womack, Marriott and their associates in Barnes Hospital (Washington University) in St. Louis, since 1930 have diagnosed and have removed five islet adenomas, and have performed three resections of the pancreas for hyperinsulinism, thus relieving patients of otherwise hopeless conditions. One of the most dramatic cases in surgical literature is Everts Graham's first subtotal pancreatectomy in a 15 months old baby, whose condition was hopeless because of mental deterioration and convulsions due to hyperinsulinism. The child has had no convulsions since the operation and his mentality, as studied by scientific tests, has improved 40 to 50 per cent. Graham and Womack are impressed with the neuro-psychiatric manifestations of hyperinsulinism. After discussing various symptoms they conclude "It is important to emphasize that in many cases the neurological and psychiatric aspects of the condition are so prominent that many of the patients with chronic hypoglycemia have been referred primarily to neurologists and psychiatrists for treatment."

About one year ago Whipple in the Presbyterian Hospital, New York, removed an islet cell adenoma from a patient who had recurring attacks of unconsciousness, and other nervous and psychic phenomena, associated with hypoglycemia, with dramatic relief of symptoms. When the staff of the Neurological Institute of the Presbyterian Hospital became "hyperinsulinism conscious" they found five similar cases upon which Whipple operated with clinical cures. Thus six persons, who were doomed to institutional lives as psychotics, or to die in hypoglycemic coma, were restored to health by the cooperation of the neuro-psychiatric and surgical staffs of one hospital. No doubt there are as many cases of hyperinsulinism passing, unrecognized and unrelieved, through the wards of every other large hospital in the country as were diagnosed and cured at the New York Presbyterian Hospital during the last 12 months.

Winans in Dallas, Texas, and Waters in Atlanta, Georgia, have reported a number of mild cases of hyperinsulinism which they relieved by dietary management. Winans in a recent paper on insomnia called attention to hypoglycemia as one of the causes of sleeplessness.

In Toronto, Howland, Campbell, Maltby, and Robinson in 1929 made the first preoperative diagnosis of an islet tumor, the removal of which cured the patient of convulsions due to "dysinsulinism" Rabinowitch, in Montreal has reported five cases of hyperinsulinism Goldzieher of New York recently reported 200 cases of spontaneous hypoglycemia Many other cases have been reported by American clinicians, and many more have been recognized and treated by physicians who have become "hyperinsulinism conscious" but have not reported their cases

Cammidge, of London, stimulated by his recognition of two cases of "chronic hypoglycemia" in 1924—an observation that no doubt was independent of the work done by others—found 198 additional cases before 1930, an average of 33 cases a year The fact that Cammidge has reported more cases of spontaneous hypoglycemia than all the other clinicians in the British Empire means simply that he learned to recognize the symptoms due to hypoglycemia and clinched his diagnoses by finding low blood sugars However, a number of cases have been reported by other British clinicians Sippe and Bostock in Brisbane, Australia have reported 30 cases of chronic hypoglycemia They regard the condition as being almost, if not quite, as frequent as the opposite condition, diabetes mellitus (hypoinsulinism) They observed hypoglycemia in 0.47 per cent of their patients, while diabetes was diagnosed in 0.51 per cent

Recently Sippe reported five cases of hypoglycemia associated with angina pectoris Cardiographic studies and blood sugar determinations showed correlation of the cardiac symptoms to hypoglycemia The cardiac attacks were prevented, or relieved, by a diet that maintained, or raised, blood sugar levels above the point at which the cardiac manifestations of hypoglycemia appeared

Personal Cases From March 1923 to May 1935 I have made the clinical diagnosis of hyperinsulinism in 119 cases, an average of 9.9 cases a year In a number of these cases the diagnosis of hyperinsulinism was made by other physicians before they referred them to us for treatment In none of these cases could we find evidence of any liver disorder that could cause hypoglycemia, though in several cases there were manifestations of dyspituitarism, in the stage of hypofunction, hypothyroidism and hypo-adrenalism which seemed to have been the primary cause of the relative, or actual, hyperinsulinism responsible for the hypoglycemic symptoms

Without question many hypoglycemic patients pass, untreated and unrelieved, through the hands of capable clinicians, because they have not become "hyperinsulinism conscious" The opinions of a number of physicians, who have had experience in dealing with hyperinsulinism, have been cited to prove that the condition, or disease entity, must be reckoned with by the medical profession It therefore seems timely to discuss the diagnosis and treatment of hyperinsulinism

Anamnesis Evidence favoring the diagnosis of hyperinsulinism may sometimes be elicited in patients who complain of "spells" of various kinds.

by inquiring as to whether the attacks occur during the night, before breakfast, or several hours after meals. If such is the case and if the patient's symptoms are relieved by taking a soft drink, fruit, or milk, or other food between meals, and if the patient feels distinctly more comfortable after meals, one would suspect hyperinsulinism. My early cases were of that type. Sometimes, however, the hypoglycemic attacks seem to occur at meals, at the sight of food, or immediately after leaving the table before there is time for digestion and assimilation of carbohydrates and when the blood sugar is still low.

Hyperinsulinism has been called the "hunger disease," because excessive appetite and the desire for food between meals are present in most cases. Sometimes, however, the patient with hyperinsulinism becomes nauseated when the attacks of weakness, nervousness and even unconsciousness occur. The patient may also complain of abdominal discomfort, relieved by taking food, his symptoms thus resembling those of gastric or duodenal ulcer. Several such cases in which operation for peptic ulcer had been considered have come under my observation.

Hunger and relief of symptoms by eating are not sufficient evidence to warrant a diagnosis of hyperinsulinism. I have seen two cases of pronounced bulimia, one in a hysterical woman and another in a mild psychotic, who obtained temporary relief from eating, but whose glucose tolerance blood sugar curves were normal.

A history of over-indulgence in sweets of all kinds is frequent in patients with hyperinsulinism. Not infrequently the victim of this condition has learned that he can relieve his symptoms by eating sweets and he devours candy and various "nick nacks," between meals to keep off attacks. After a time sweets give relief for only a few minutes. Often such patients will voluntarily mention that they "crave sweets." Occasionally hyperinsulinism patients will go on "sugar sprees" when they will eat inordinately of cakes, candy, pies, ice cream and other cane sugar products for a few days. Usually their symptoms are aggravated by such overindulgences.

Overindulgence in Sweets and in Caffeine Beverages My first case of hyperinsulinism observed 12 years ago gave a history of overindulgence in caffeine beverages. Since then the history of taking coca-cola, or coffee, between meals for the relief of the attacks of hypoglycemia, or to prevent them, has occurred too frequently not to have a relationship of cause and effect, at least the symptoms are exaggerated by the frequent use of soft drinks between meals. The caffeine soft drinks relieve the symptoms temporarily, first, by supplying a soluble carbohydrate that is rapidly absorbed and metabolized, and second, as Womack suggested, probably by the stimulation of the adrenals by caffeine, thus raising the blood sugar level above the point at which the hypoglycemic symptoms occur.

A good therapeutic test for hyperinsulinism is to give the patient a glass of coca-cola, or a cup of coffee without cream, during an attack, or before the suspected attack. If it relieves the symptoms temporarily or prevents

the attacks, hyperinsulinism may be suspected. Certainly there is not a better or quicker acting remedy for an attack, or for symptoms of hypoglycemia, than a glass of coca-cola or other caffeine-containing soft drink, or a cup of coffee, with sugar but without cream. The regular excessive use of the caffeine beverages, however, seems to exaggerate the hypoglycemia in patients with hyperinsulinism.

Gastrointestinal Manifestations The gastrointestinal manifestations of hyperinsulinism are frequent and varied. A considerable proportion of the patients who have hypoglycemic symptoms associate their discomfort with food. Often they feel that certain articles of food they had eaten previous to attacks were responsible for their symptoms. Many such patients complain of hunger, but sometimes they suffer from sitophobia because of the fear that eating will make them worse.

Many patients who have come to our clinic complaining of "nervous indigestion," or with a previous diagnosis of "irritable colon," have been found to have hypoglycemia that synchronized with their symptoms, and have been relieved by a diet planned to keep blood sugar levels within normal limits. Other patients, with actual duodenal ulcers, have had associated nervous symptoms which were proved to be due to hypoglycemia. It, therefore, should be remembered that hyperinsulinism may coexist with actual lesions of the stomach and other abdominal viscera.

Cambridge in reporting 200 cases of "chronic hypoglycemia" said "Comparatively few cases of hypoglycemia are free from gastrointestinal disorders." Sippe and Bostock mentioned gastrointestinal symptoms in 18 of 25 reported cases of "chronic hypoglycemia," most of them mild cases that were promptly relieved by dieting. Many other clinicians have reported cases of hyperinsulinism, or chronic hypoglycemia, in which gastrointestinal symptoms were present.

Dextrose tolerance tests, carried out for six full hours, in patients with complaints referable to the gastrointestinal tract, associated with nervousness and weakness, may reveal hypoglycemia as the cause of the symptoms.

Abdominal Pain Evarts Graham observed abdominal pain in his first case of islet cell adenoma of the pancreas. The patient had had his appendix removed without relief from the abdominal pain. Abdominal pain, however, is by no means a constant symptom in the severe cases of hyperinsulinism with, or without, adenomas of the pancreas. Womack writes "In two of eight cases, five adenomas of the pancreas and three resections successfully operated upon in Barnes Hospital, pain in the abdomen was outstanding. A cholecystectomy was done in one elsewhere and an appendectomy in the other with no relief. This cramp-like pain disappeared with the relief of the hypoglycemia." Undoubtedly many unnecessary and unsuccessful abdominal operations have been performed upon hyperinsulinism patients.

The location of the pain is important. In the cases of hyperinsulinism that I have seen, in which abdominal pain was a symptom, the pain was in

the mid-portion and upper left quadrant of the abdomen. In most of them there was tenderness on deep pressure in the same locality, i.e., over the pancreas. Periodicity of the pain, usually more pronounced when the stomach was empty, was present in a number of cases. Partial resections of the pancreas relieved the pain in three of my cases.

Attacks of Convulsions and Unconsciousness The most important manifestations of the severe types of hyperinsulinism are attacks of unconsciousness and convulsions. Most of the patients with hyperinsulinism who have been operated upon have had varying periods of unconsciousness, with and without convulsions, and many of them have been diagnosed as epilepsy, until blood sugar studies proved the presence of a sufficient degree of hypoglycemia to account for the convulsions and unconsciousness.

Convulsions do not occur in all severe cases of hyperinsulinism. Frequently attacks of unconsciousness resembling diabetic coma occur. Several cases of death in hypoglycemic coma without convulsions have been reported and the diagnosis was proved by finding at autopsy tumors of the islands of Langerhans.

The unconsciousness following hypoglycemic convulsions lasts from a few minutes to several hours. In one case of repeated convulsive attacks, in which the patient was in what was called "hypoglycemic status epilepticus" a clinical cure resulted from the removal of a carcinoma of the islands of Langerhans (Bast, Schmidt and Sevringhaus). Often patients with hyperinsulinism awaken voraciously hungry after convulsions, but not always, because nausea and vomiting sometimes follow hypoglycemic attacks.

Hysterical and Psychotic Manifestations Many patients who have been regarded as hysterical, or psychasthenic, have been proved to suffer from hyperinsulinism, and have been clinically cured by regulation of the diet.

Actual psychotic symptoms may occur in the severe cases of hyperinsulinism. The woman, reported by Finney and Finney, had "crazy spells" when she would do queer things. She was found to have a blood sugar of 0.030 per cent. Graham and Womack reported cases in which patients with hyperinsulinism had actual psychoses which subsided after removal of islet cell adenomas of the pancreas. Many other clinicians have observed psychotic patients who had hyperinsulinism.

Powell suggests that the protean nervous manifestations in hyperinsulinism are due to a deficiency of glucose in the blood supply of the brain. He cites a recent editorial in the *Journal of the American Medical Association* to the effect "that the brain lives exclusively on a sugar diet and that the quantity thereof may readily be determined by various blood sugar and glucose tolerance tests." Zeigler says that spontaneous hypoglycemia will cause insomnia and maniacal delirium.

DIAGNOSIS

A positive diagnosis of hyperinsulinism either of the mild or severe type cannot be made without fasting blood sugar studies and glucose tolerance tests proving the presence of hypoglycemia in a patient with symptoms of hyperinsulinism

Routine fasting blood sugars on my patients for the last 12 years have shown hypoglycemia in many whose history did not suggest hyperinsulinism, but who, on more careful questioning, gave definite hypoglycemic symptoms. In my first case of epilepsy associated with hyperinsulinism the diagnosis was not suspected until his fasting blood sugar, taken as routine, was found to be 0.060 per cent. Attention having been called to the low fasting blood sugar in this case, further questioning brought out a history of hypoglycemic symptoms, and then a glucose tolerance test showed a low flat hyperinsulinism curve.

Repeated Blood Sugar Studies One fasting blood sugar or one glucose tolerance test is not always sufficient to warrant a positive diagnosis of hyperinsulinism since there seem to be periods when the hyperinsulinism patient will have normal blood sugar readings, even though at other times he has shown marked hypoglycemia. Cushing observed in hyperpituitarism that there are undulations, or waves of accelerated hypophyseal secretion, and it is quite evident that in hyperinsulinism there are quite marked variations in islet cell secretion.

The factor of mental and physical fatigue affects blood sugar levels. In making glucose tolerance tests, ambulatory patients should not be permitted to lie down, but should, if possible, take about the same amount of exercise that they ordinarily take when the attacks have occurred. I have observed repeatedly in patients taking the glucose tolerance test that when the blood sugar levels became low, they had hypoglycemic symptoms which subsided when they lay down. After resting for a few minutes without taking food, the blood sugar readings were higher.

The occurrence of the symptoms complained of, at the stage of the test when the blood sugar becomes low, as frequently occurs, is presumptive evidence of hyperinsulinism. So likewise is the finding of a low blood sugar in blood drawn during a spontaneous attack. It, therefore, is advisable to get repeated blood sugar tests an hour before the noon and evening meals and after the patient has had several hours' work at his usual vocation at about the time symptoms usually occur. In studying patients with a history of epileptic or epileptiform attacks, blood sugar tests should be made at about the time of expected attacks, but it should be remembered that after generalized convulsions usually the blood sugar readings will be higher than before the paroxysm.

Gammon and Tannery suggested that in examining the patient suspected of having hyperinsulinism sufficient insulin be given to produce hypoglycemic reactions which in many cases will reproduce the patient's symptoms.

Since in many cases the same result may be accompanied by reproducing the symptoms in the hypoglycemic phase of glucose tolerance tests, the use of insulin as a diagnostic measure seems rarely indicated

The Six Hour Glucose Tolerance Test The glucose tolerance test should be carried out for six full hours in making the diagnosis of hyperinsulinism. I have observed a number of patients whose blood sugar readings were normal for four hours after the ingestion of the dextrose, but fell rapidly and to very low levels in the fifth and sixth hours. Recently a patient who had marked symptoms of hyperinsulinism and had shown a hyperinsulinism curve was given a glucose tolerance test in another hospital. The test was carried out for only four hours, the last reading having been 0.070 per cent, on this evidence the case was not diagnosed as hyperinsulinism. Four hours is long enough to carry out a glucose tolerance test for diabetes, but six or eight hours may be necessary in studying the case for suspected hyperinsulinism. If glucose tolerance tests were carried out for six hours, they might show, as they did in a few of my cases, a diabetic curve for three or four hours and hypoglycemic readings for the fifth and sixth hours.

Patients object to and sometimes refuse venipunctures for blood specimens every hour for six hours, and laboratory technicians sometimes get tired of running blood sugars, but unless the test is carried out that long, some cases of hyperinsulinism will not be diagnosed as such. Sometimes it is difficult to get into the veins in making glucose tolerance tests, and then it is best to get the fasting blood sugars and the blood sugar five and six hours after the ingestion of the dextrose.

Therapeutic Test If for any reason the patient cannot or will not have blood sugar studies made and if hyperinsulinism is suspected, a few days of rest on a relatively low carbohydrate diet consisting largely of the 5 and 10 per cent vegetables and fruits, with orange or tomato juice on arising and on retiring and every one or two hours between meals and when awake at night, may relieve the symptoms. If the patient is underweight, two to four ounces of cream may be given every three hours when awake. The cane sugar products and other soluble carbohydrates including soft drinks and candy between meals should be given only to relieve the attacks. On such a diet with sufficient rest, the patient with all but the most severe hyperinsulinism will be improved or completely relieved of his symptoms. If he is not relieved either his symptoms are not due to hyperinsulinism or blood sugar studies may show hypoglycemia of sufficient degree to demand exploration of the pancreas for an adenoma.

The Diagnosis of Hypoglycemic Coma It should be a routine in every case of unexplained unconsciousness to make a blood sugar determination at the earliest moment possible. Hypoglycemic coma is one of the frequent causes of unconsciousness, particularly when preceded by convulsions. Wanchope recommends the use of adrenalin hypodermatically, and dextrose intravenously in the cases in which there is the question of diabetic or hypo-

glycemic coma If the unconsciousness is due to hypoglycemia the adrenalin and the dextrose intravenously will bring the patient out of the coma in a few minutes, whereas if the patient continues unconscious a delay of 15 minutes while waiting for a blood sugar report will not affect the ketosis which usually can be relieved by the use of insulin

DIFFERENTIAL DIAGNOSIS

Every possible cause of hypoglycemia besides pancreatic disease should be considered, including studies of all the other organs of internal secretions, so as to exclude them as factors if possible, before making a diagnosis of uncomplicated hyperinsulinism

Since hyperinsulinism has been manifested by symptoms which have suggested hysteria, psycho-neurasthenia, neuro-circulatory asthenia, psychoses, brain tumors, epilepsy, narcolepsy, status epilepticus, epileptiform convulsions, appendicitis, gall-bladder infection, duodenal ulcer and many other diseases it is apparent that in the study of all patients presenting such symptoms blood sugar tests should always be included On the other hand the finding of hypoglycemia does not always prove that it is the cause of the symptoms We have had two cases of brain tumor in which hypoglycemic symptoms were pronounced

Hyperinsulinism is invariably associated with hypoglycemia It should be remembered, however, that in patients who have hypoglycemic symptoms, fasting blood sugars are not always low Therefore, repeated and varied blood sugar studies should be made before hypoglycemia is excluded in suspected cases of hyperinsulinism It should be remembered also that the patient with hyperinsulinism may have other diseases that may, or may not, affect the hypoglycemic symptoms Thus, two cases of hyperinsulinism in syphilitic patients have been observed in which anti-syphilitic treatment did not affect the blood sugar levels or the symptoms of hypoglycemia

Hypoglycemia from Extra-Pancreatic Disorders Cases of marked degrees of hypoglycemia due to organic diseases or functional disturbances of other organs besides the pancreas have been reported as having been due to (a) a deficient glycogenesis in the liver from poisons such as arsphenamine or other arsenicals, phenylhydrazine, phosphorus or other hepatotoxins (Cross and Blackford), and from massive tumor of the liver (Nadler and Wolfer), (b) inadequate mobilization of glycogen due to deficient secretion of the suprarenals (Anderson), (c) pituitary dysfunction (Josef Wilder), (d) thyroid dysfunction (Tedstrom) The case of Weil, in which the hypoglycemic convulsions occurred only during menstruation suggests that ovarian dysfunction may be a factor in some cases

It is of particular importance to exclude hypopituitarism, hypothyroidism, and hypoadrenalinism which may be the primary cause of the hypoglycemia that is responsible for the symptoms of hyperinsulinism The secretions of the hypophysis, thyroid and adrenals are antagonistic to, and therefore may control, the secretion of insulin,

TREATMENT

The problem of dieting in hyperinsulinism is much the same as in diabetes mellitus (hypoinsulinism) in that each patient has to be dieted to suit his particular needs. It is necessary to arrange a diet that will nourish the patient properly, providing sufficient amounts of carbohydrates, proteins and fats, with due consideration to its vitamin content. As far as the quantity is concerned, it should have a lower carbohydrate content than in diabetes, with sufficient calories to maintain normal body weight and physical vigor. The protein content should depend on the age and weight of the individual, we give from 60 to 75 gm. to an adult weighing 70 kilograms.

Theoretically, a high carbohydrate diet would seem to be indicated in hyperinsulinism, but John pointed out that carbohydrates stimulate the secretion of insulin and that when rapidly soluble carbohydrates such as sugars are given, they cause excessive insulogenesis, which continues after the carbohydrates are metabolized, with resulting hypoglycemia. John observed, in giving dextrose tolerance tests, that while the blood sugar level was high for the first one or two hours, it was followed by a rapid fall to a level much lower than the fasting blood sugar. I made the same observation independently after giving a dextrose tolerance test to my second patient with hyperinsulinism in 1923.

Weil's experience with his patient with dysinsulinism, who had recurring attacks of convulsions and unconsciousness, proves the fallacy of a diet high in soluble carbohydrates in insulogenic hypoglycemia. He found that a few hours after a high carbohydrate meal, the blood sugar reached a much lower level than the patient's fasting blood sugar. He was able to control the attacks of convulsions by placing the patient on a low carbohydrate, high fat diet with frequent feedings.

Shepherdson states that the blood sugar level will rise on a low carbohydrate, high fat diet. He quotes Weeks, Renner, Allan and Wishart as having observed in a study of epileptic patients on high fat diets that in every case they developed a hyperglycemia. It is possible that ingested fats may have a direct effect in inhibiting the secretion of insulin and that, in the cases of epilepsy associated with hypoglycemia in which the ketogenic diet has proved beneficial, perhaps in some cases the good effects have been due to a rise in the blood sugar level, rather than to the sedative action of the ketone bodies in the blood. Certainly in my hands a moderately low carbohydrate, high fat, moderate protein diet has given the best results in treating chronic hyperinsulinism.

Low Carbohydrate, High Fat Diets Early in my experience in dealing with hyperinsulinism I began using a low carbohydrate diet, consisting largely of 3, 5 and 10 per cent vegetables and fruits, combined with a high proportion of fats, with frequent feedings. I reasoned that the carbohydrates in the form of vegetables and fruits, which must be digested before being absorbed and metabolized would be released as dextrose in small

quantities at a time, and therefore, would not stimulate the secretion of insulin as much as meals made up largely of foods of high carbohydrate content, particularly those containing cane sugar products. Fats, particularly cream, were given with meals and between meals, with the idea that they are emptied slowly from the stomach. Therefore, the metabolism of the carbohydrates mixed with fats would be slow compared to the rapid emptying of the stomach and the accelerated metabolism after the ingestion of carbohydrate meals without fats.

Waters, basing himself upon the experimental studies of Sweeney, which showed higher blood sugar levels after high fat diets, and lower levels after high carbohydrate diets, and also upon his own experience in relieving cases of spontaneous hypoglycemia by a high fat, moderately low carbohydrate diet, concluded "A diet reducing the carbohydrate intake and increasing the volume of fats seems to diminish an excessive insulin production and to raise the blood sugar level."

Dieting the Hyperinsulin Individual The diet in each case of hyperinsulinism should be calculated to meet the patient's nutritional needs. The adult patient with hyperinsulinism, of average height and weight, should have about 2,250 calories, derived from 90 to 150 gm of carbohydrates, from 60 to 75 gm of proteins and the remainder from fats, largely cream and butter. The food intake is best divided into from five to seven feedings a day.

A number of my patients with hyperinsulinism have been overweight, and other clinicians have observed a number of obese patients with hyperinsulinism. In such cases the fats should be reduced, and a low caloric diet with food every two hours is indicated. In such cases I prescribe a diet of about 120 gm of carbohydrates, 60 gm of fat and 60 gm of protein (1,260 calories) divided into six or eight feedings a day. On such a diet the patient's activities should be restricted and the amount of carbohydrates should be increased to 150 to 200 gm, or even more if the patient is losing weight, or if he becomes weak.

In the underweight, asthenic patient with hyperinsulinism, a diet of 90 to 150 gm of carbohydrate, from 200 to 300 gm of fat, and from 60 to 75 gm of protein, divided into five or six feedings a day, will keep the blood sugar at a sufficiently high level to prevent hypoglycemic symptoms, and will build up the patient's general health and state of nutrition.

Careful blood sugar studies should be made on each patient for a few days after being placed on a diet for hyperinsulinism, during which time his food should be weighed and measured if possible. It is just as necessary to teach the patient with hyperinsulinism food values and to calculate and arrange the menus suited to his particular case, as it is to teach "diabetic arithmetic" to patients with hypoinsulinism (diabetes mellitus). The intelligent patient with severe hyperinsulinism usually becomes very much interested in "playing the game of dieting" because he has a holy dread of the attacks of unconsciousness, with or without convulsions.

It is essential to impress the patient with hyperinsulinism with the necessity of moderation in all things, particularly physical exercise. Studies on marathon runners by Levine and his associates showed that physical exhaustion produces physiologic hypoglycemia. A number of my patients have observed that their attacks of hunger, weakness and the like, and even petit mal and grand mal seizures, have occurred most frequently after physical exertion. The patient with hyperinsulinism should be taught all the rules of personal hygiene adapted to his particular needs, just as the diabetic patient is taught how to live and enjoy health even though he has the handicap of a crippled pancreas.

The Use of Bromides and Barbiturates in Hyperinsulinism The dietary management of hyperinsulinism, without medicines, usually is sufficient to control the disease and prevent hypoglycemic symptoms in the mild types and in many of the severe cases, yet drugs may be required at times in the more serious cases, particularly in those associated with epileptiform convulsions.

The rationale of the use of the bromides and barbiturates in epilepsy is considered to be their effect as motor depressants, thus preventing the convulsions. We are studying, as clinical material becomes available, the question as to whether these drugs may have some effect in raising the blood sugar in severe hyperinsulinism. The bromides are not advised in the treatment of hyperinsulinism, even when it is associated with epilepsy, except as a temporary measure. The bromism that follows the use of the bromides when used over a long period of time may be more harmful to the epileptic patient with hyperinsulinism than the convulsions. Phenobarbital in $1\frac{1}{2}$ grain (0.1 gm.) doses night and morning and in the most severe cases after the noon meal is the least harmful drug now known that will control the epileptic convulsions, and it is helpful in cases of severe hyperinsulinism in patients who cannot, or will not, follow a prescribed diet. Phenobarbital may be used in conjunction with dietary management in cases that are difficult to control.

Belladonna Having in view the possibility that belladonna might inhibit the secretory activity of the islet cells, I have used it in my mild cases of hyperinsulinism for several years, at times with seemingly good results.

Evans and his associates report the discovery of a diabetogenic hormone from the anterior pituitary, which will raise blood sugar. As yet this hormone has not been separated from the growth, and perhaps other, hormones, but there seems reason to hope that a purified product of the diabetogenic hormone will be available for use in hyperinsulinism in the near future.

Suprarenal Products Adrenalin (1 c.c. of 1-1000 solution) given hypodermatically will raise blood sugar, and in hypoglycemic coma may restore consciousness in a few minutes, but its effects are temporary and it is not of value in hyperinsulinism except in the attacks. Adrenalin has no effect when given orally, and it is questionable if any of the preparations

of suprarenal medullary substance are of value if given by mouth. Nielsen and Eggleston, however, credited a whole gland product of the suprarenals with a part of their successful treatment of three cases of epileptiform convulsions due to "dysinsulinism."

Ephedrine Ephedrine has been used successfully in the treatment of narcolepsy. Ephedrine mobilizes glycogen and, combined with diet and rest, may maintain the blood sugar level at a point high enough to prevent hypoglycemic symptoms. Ephedrine was used with doubtful results in two of our cases of epilepsy with hyperinsulinism.

Thyroid Extract Since hypothyroidism is sometimes associated with hyperinsulinism, thyroid extracts would seem to be indicated in the cases in which the basal metabolic rate is low. Tedstrom, and Evans and McDonough used thyroid extracts with benefit in the treatment of some of their cases of hyperinsulinism with low basal metabolic rate.

Insulin John reports having used insulin with excellent results in the treatment of hyperinsulinism. He is of the opinion that if exogenous insulin is given hypodermatically after meals before the postprandial blood sugar rise stimulates the secretion of insulin, the amount of endogenous insulin will be sufficiently reduced so that the hyperinsulinism patient will not become hypoglycemic several hours after meals. John gives from 10 to 20 units of insulin after meals and presents blood sugar records before and after the insulin was used, which seem to justify his conclusions. I have used insulin in two cases of hyperinsulinism with apparently good clinical results, though blood sugar studies were not made to prove that the blood sugar levels were higher after the use of insulin.

Deep Roentgen-Ray Therapy Barrow has used deep roentgen-ray therapy in the treatment of hyperinsulinism with reported good results. He believes that the irradiation over the pancreas may reduce the secretion of insulin just as it sometimes ameliorates the symptoms in hyperpituitarism with or without adenomas, presumably by decreasing hypophyseal secretion. In view of possible dangerous secondary irradiation of the liver, stomach, duodenum and other neighboring organs, this therapeutic method should be used with great caution in attempting to decrease insulin secretion. Sippe and Bostock quote Terbruggen and Heinlein as having "produced a lethal hypoglycemia in rabbits by irradiation of the pancreas." The external secretory portion of the organ, involved in producing trypsin, amylase and steapsin showed degenerative changes, whereas the islands of Langerhans were well preserved or even hypertrophic. Mosenthal also mentions irradiation of the pancreas as having caused hypoglycemia.

SURGERY IN HYPERINSULINISM

While the mild and moderately severe, and many of the very severe cases of hyperinsulinism can be relieved by dietary management, as certainly as diabetes mellitus can be controlled by diet and the use of insulin, in an oc-

casual case surgery offers the only hope of relief. The question then arises: When is surgery indicated in hyperinsulinism?

It should be stated emphatically that in no case of hyperinsulinism should surgery be resorted to until the patient has given a full trial to properly directed dietary management. Haphazard dieting in hyperinsulinism gives as unsatisfactory results as unscientific methods in the management of diabetes mellitus, so that the patient with hyperinsulinism has not had the best chance to control his disease unless he has been kept, for a few weeks at least, on a weighed and measured diet calculated and prescribed to suit his individual needs. If the hyperinsulinism patient cannot control his symptoms by properly directed dieting then surgery should be considered.

It is an interesting fact that of the 40, or more, operations on the pancreas for hyperinsulinism all but two have been performed by surgeons in the United States and Canada. There has not been a death reported from pancreatic operations performed in the United States, though I have heard of two deaths which resulted from operation that have not been reported. The only two operations on the pancreas for the relief of hyperinsulinism that have been reported, besides the American cases, were performed in Russia, both died from the operations. In one of these, a large adenoma of the pancreas, the growth had reached the stage where it was inoperable.

Criteria for Exploratory Operations An exploratory operation for the relief of hyperinsulinism should be considered

- 1 In the acute fulminating cases which develop rapidly and in which hypoglycemic attacks with convulsions and unconsciousness cannot be controlled by intravenous dextrose therapy, and in which death seems imminent.

- 2 In the severe chronic cases that cannot be controlled by properly directed dietary management in a few weeks.

- 3 In cases with severe neuro-psychiatric symptoms of long standing in which on account of economic or social or psychic handicaps the diet cannot be carried out properly, or long enough to permanently benefit the patient.

Surgery of the pancreas is contraindicated in primary disease, or hypofunction, of the anterior pituitary, the thyroid, or the adrenals, resulting in relative, or actual, hyperinsulinism, for the obvious reason that such operations could not remove the cause of the hypoglycemic symptoms. Likewise no benefit could be expected from surgery in hypoglycemia resulting from acute yellow atrophy of the liver, massive carcinoma of the liver, or the hepatic lesions that follow acute poisoning from hepatotoxins such as arsenophenamine, phenylhydrazine and the toxic varieties of mushrooms.

The Diagnosis and Treatment of Insulomas If it were possible to diagnose an islet cell adenoma or carcinoma before operation there would be no need for trying the patient on a diet, because in such cases surgery will give almost certain relief unless delayed until the neoplasm has advanced to the stage when metastases make the case an inoperable one. One of the most brilliant chapters in American surgery will be written when the results of operations on the pancreas for islet cell tumors have been recorded.

Unfortunately no one as yet has established the criteria necessary for diagnosing insulomas. Gammon and Tennyson summarize what is known regarding the differentiation between hyperinsulinism resulting from the neoplasms of the islands of Langerhans and the manifestations from functional insulogenic hypoglycemia, as follows: "All that can be said is that there is perhaps a tendency for the disease (hyperinsulinism) to be more rapid in its development, more severe in its manifestations, more erratic in behavior and more likely to cause death when tumor is present than in functional hypertrophy of the islands."

If an exploratory operation on a patient suffering from hyperinsulinism reveals an adenoma, or carcinoma, of the body or tail of the pancreas it should be removed, if possible. In one of Evarts Graham's series an islet adenoma the size of a baseball was removed from a psychotic patient with a clinical cure for two years, without any present indication of recurrence. If there are metastases in the liver and extensive involvement of the surrounding structures the case is inoperable.

In making an exploration for an adenoma of the pancreas it should be remembered that some of those found have been quite small, yet their removal completely cured the patients of hypoglycemic symptoms. Smith and Seibel found at autopsy an adenoma in the head of the pancreas less than 1 cm. in diameter, yet the patient died in hypoglycemic coma. It therefore should be remembered that even an exploratory operation may not reveal the adenoma that is causing severe hypoglycemic symptoms.

It should not be forgotten that though adenomas of the islands of Langerhans are usually single, two or more may be found in the same patient, and the removal of one may not relieve the patient of his symptoms. Evarts Graham in one case operated on a patient who had severe hypoglycemic symptoms and he removed an adenoma from the anterior surface of the body of the pancreas. The symptoms continued unabated. Later the second operation by Graham revealed another adenoma on the posterior surface of the body of the pancreas. The removal of the second tumor relieved the symptoms.

Resections of the Pancreas in Hyperinsulinism If an exploratory laparotomy on a patient suffering from hyperinsulinism does not reveal an adenoma or other operative lesions, but a normal appearing pancreas, should a resection be performed? As yet there are no criteria for performing resections of the pancreas in hyperinsulinism. Each case will have to be considered from its various aspects before deciding to resect a major part of the pancreas, or to close up the abdomen and give the patient another chance at dieting.

A brief review of some of the reported cases may provide data that should be helpful to the surgeon in making his decision in such a case.

The first resection of the pancreas for hyperinsulinism was performed in 1928 by Finney and Finney, who removed about three-fourths of the pancreas from a psychotic patient referred to them by Barker and Sprunt.

There was definite improvement, but not complete relief, though the blood sugar levels were higher following the operation. Six years later this patient committed suicide.

The next resection of the pancreas for hyperinsulinism was performed by Holman, with temporary relief of symptoms. This case was subsequently explored by Judd, who resected another portion of the pancreas with some relief, but the symptoms recurred.

Experience with Eight Cases of Surgical Hyperinsulinism I have advised surgical intervention in seven cases of hyperinsulinism. In three cases resections of from one-half to five-sixths of islet bearing tissue of the pancreas resulted in clinical cures. In two cases of epilepsy associated with hypoglycemia resection was followed by slight improvement, and in one case in which there was a history of probable dyspituitarism resection of five-sixths of the pancreas failed to control the epileptic attacks or the hypoglycemia. In the seventh case the abdomen was closed without resection of the pancreas after an exploratory laparotomy which revealed a normal appearing pancreas. This patient since the operation has adhered more rigidly to his diet and has shown a lessened frequency of his attacks of convulsions. The eighth case in which I advised operation was a patient of Dr J. E. Beck and Dr G. O. Segrist of Mobile. They had made a diagnosis of hyperinsulinism from very low blood sugar readings in a man who had been incapacitated for work for a year or more because of recurring periods of unconsciousness. The patient was violently psychotic at times. On account of the severity of the symptoms a tumor was suspected and I advised that the patient be sent to Dr. Evarts Graham of St. Louis, who operated, removing a large islet tumor. The patient made a complete recovery. He has had no symptoms in two years and is working regularly.

CONCLUSIONS

- 1 Hyperinsulinism, or spontaneous hypoglycemia, is a frequent and widespread disease, numerous cases having been reported by discriminating clinicians in many countries.

- 2 The manifestations of hyperinsulinism are protean, and identical with the symptoms that have been reported from overdoses of insulin in the treatment of diabetes mellitus.

- 3 The anamnesis is important in making the diagnosis of hyperinsulinism in the mild cases. Usually, there is a history of attacks of weakness, nervousness, trembling and sweating before breakfast, one or two hours before noon and evening meals, before retiring and often during the night. The attacks are relieved by taking food. In the more severe cases in addition to the mild symptoms, there is a history of recurring attacks of unconsciousness and convulsions, or hysteria. Neuropsychiatric, gastrointestinal and cardiac symptoms may be pronounced.

4 Low blood sugar readings, before breakfast, one or two hours before meals and in attacks, and the occurrence of a hypoglycemic phase in dextrose tolerance tests, are necessary for proof that the symptoms are due to spontaneous hypoglycemia. Dextrose tolerance tests should be carried out for six full hours before excluding the diagnosis of hyperinsulinism. The symptoms may, or may not be, reproduced in the hypoglycemic phase of dextrose tolerance tests.

5 The secretory interrelations of the pituitary, thyroid and adrenal glands with the insular apparatus of the pancreas should be considered carefully before making a diagnosis of uncomplicated hyperinsulinism. Likewise, hypoglycemia from deficient glycogenesis should be excluded before making a diagnosis of hyperinsulinism.

6 The great majority of cases may be relieved by a moderately low carbohydrate, high fat diet with frequent feedings between meals, and at night if there are nocturnal symptoms. The diet should be prescribed to meet the individual needs of the patient under treatment.

7 Surgery offers relief in cases that cannot be relieved by properly directed and carefully carried out dieting over a period of a few weeks or months. The removal of insulomas, either adenomas or carcinomas, of the islands of Langerhans has resulted in clinical cures. Resection of the pancreas relieved the symptoms in about 50 per cent of reported cases.

8 Two fatal cases of islet cell carcinomas have been reported which were inoperable because of the size of the tumors and the presence of liver metastases. It, therefore, is important to make the diagnosis of hyperinsulinism early before the neoplasm of the islands of Langerhans has progressed to the inoperable stage.

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MASSIVE DOSES OF VITAMIN D IN THE TREATMENT OF PROLIFERATIVE ARTHRITIS ^{*}

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RECENT interest in the treatment of arthritis, by massive doses of vitamin D,¹ has been sufficiently great to warrant a clinical trial of this mode of therapy in a group of patients with the chronic proliferative (infectious) type. Past experience of disappointing results when such recommended therapeutic agents as gold and sulphur were used over an adequately long period under controlled clinical conditions had rendered us somewhat skeptical but it appeared worthwhile, however, to determine if vitamin D might constitute a valuable adjunct to a composite program of treatment in this group of diseases.

Thirty-eight patients having chronic infectious or proliferative arthritis and two patients in the same group, but with histories of earlier rheumatic fever, were selected. These patients had been under observation for at least six months and six complete clinical and laboratory check-ups had been made. It was possible thereby to contrast their progress before and after the administration of large doses of vitamin D. In evaluating any therapeutic agent in the treatment of arthritis, such a control is more valuable than is a study of parallel groups (one with and one without the test treatment). Comparison before and after institution of the use of a given therapeutic agent in well-studied patients is of greater value in our experience than the analysis of data from treated and non-treated groups.

The indications for the use of massive doses of vitamin D are considered to be the presence of proliferative arthritis and, inasmuch as the work was experimental, no special selection was employed among members of this group, other than that any patient was eliminated whose general condition was such that a severe reaction might be disastrous.

Later, it became evident that the presence of a very sensitive colon contraindicated the use of the vitamin in large quantities. In general it was found that the type of arthritic patient for whom vaccine is indicated, that is, a patient in whom desensitization seems to be the main problem, was decidedly not the type in which to use massive doses of vitamin D. When a high sedimentation and low agglutination titers were taken to indicate the desirability of the employment of streptococcus vaccine, then the use of massive doses of vitamin D seemed inadvisable.

The method employed in this work had as its first step the evaluation of clinical progress and laboratory changes in each patient up to the time of administration of vitamin D. After this base line in degree of progress for

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six months was established massive doses of vitamin D with supplementary medication (vitamin B and calcium) were instituted and similar studies of the patient continued to see if more definite progress toward recovery would result

The dose employed was never increased over 300,000 units of vitamin D daily and the ordinary dose most often used was 200,000 units daily. Under no circumstances did we see reason to increase the dose to the enormously high levels that have been reported by some workers.

The sources of vitamin D were as follows: irradiated ergosterol in sesame oil supplied for experimental purposes by the National Institute of Nutrition, Los Angeles; viosterol and vitamin D in propylene glycol.

The supplementary medication employed consisted of a good source of vitamin B, such as wheat germ or brewer's yeast and calcium supplied in the form of dicalcium phosphate and milk.

The additional treatment of these patients consisted of a definite regimen used in this Clinic. This treatment may be briefly summarized: Adequate rest, physiotherapy, heliotherapy, dietotherapy, treatment or early removal of foci, blood transfusions, orthopedic measures and intravenous bacterial antigen. Obviously, under such a program, there were individual variations. However, these were minimized as much as possible.

The results of treatment in 40 patients were evaluated in two ways. First, clinical improvement, such as diminution in joint pain, swelling and stiffness, increase in general strength, appetite and weight, was noted; second, laboratory changes were studied once a month and included the determination of the sedimentation rate, agglutination reactions for streptococci, morphological blood picture and the level of calcium and phosphorus content of the serum.

The percentage of clinical improvement noted was considered definite and clear-cut in 20 per cent, i.e., in eight patients in this series we could detect a definite progressive increase in appetite, weight, general feeling of strength and a decrease in joint swelling, pain and stiffness. Similarly, in eight patients, or 20 per cent of the total series, it was necessary to abandon the treatment entirely on account of unfavorable reactions.

One patient complained of violent persistent nausea for four days, intense headache and profuse sweating. In another patient, severe diarrhea was the only evidence of a reaction, but necessitated the withdrawal of the therapeutic agent. Reactions in the remaining six were vague conditions developing in the first week of treatment characterized by beginning loss of appetite, drowsiness, slight headache often present on awaking in the morning but worse with the advance of day. However, the symptoms in the latter disappeared in about 48 hours following the stopping of vitamin D.

The remaining 60 per cent, or 24 patients out of the 40 treated, during the period of our observation, showed no definite benefits that could be attributed to vitamin D therapy.

In more than half of the patients, therefore, vitamin D concentrates did not seem to hasten recovery. It should be borne in mind in this connection, however, that treatment problems in chronic proliferative arthritis are so complicated and so manifold in their aspects that we are hesitant to say at the present time that some of these 24 patients, during the next few months, may not show some improvement due in part to their vitamin D therapy.

From a study of over 500 cases the base line for the laboratory changes in patients under treatment in this Clinic is well established and in this series studied with the use of vitamin D no significant departure was observed. For example, the morphological blood picture did not alter in these patients more rapidly or more distinctly in general than it does in other patients being treated without vitamin D. Calcium and phosphorus determinations exhibited only minimal changes, the average increase in calcium content of the serum being 0.75 to 0.95 mg. All determinations were within normal limits. There was no significant change in the calcium phosphorus ratio noted.

These results may be briefly summarized as follows. On a composite program of therapy 40 patients with chronic proliferative arthritis received massive doses of vitamin D. Out of this group eight were definitely improved clinically, eight exhibited more or less severe reactions, the remainder exhibited no improvement attributable to the medication. The laboratory tests employed to follow the progress of these cases did not show any significant changes.

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CASE REPORTS

ARTHRITIS PSORIATICA, REPORT OF A CASE *

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THIS case of psoriasis and destructive bone and joint changes is reported because the pathological process of the bones and joints is of an unusual character

CASE REPORT

M G, housewife, 57, native born, of Irish extraction, was admitted to the Psychiatric Clinic of the Institute of Human Relations, December 26, 1934, with a history of psoriasis and of multiple joint involvement leading to mutilating deformities of the hands and feet—the skin and joint conditions having both begun about 20 years ago. The reason for admission to the Psychiatric Clinic was that the patient had a psychosis of three months' duration characterized by depression, agitation, suicidal tendencies, somatic and self-accusatory delusions, and auditory and visual hallucinations, this mental condition was diagnosed by the staff as one of agitated depression (involuntional melancholia). After about three months she was transferred to the Norwich State Hospital, the mental condition unchanged. Prior to the onset of the psychosis the patient had been considered a normal individual and had made a satisfactory adjustment to the environment in the face of a chronic and serious physical handicap.

Family History The paternal grandmother died at the age of 92, of "arthritis." Beyond the fact that she had been unable to walk for 10 years prior to her death, no details were obtained concerning the nature of the supposed arthritis. The family history shows no other instances of rheumatic disease and is non-contributory in other respects.

Past History The birth and early development are considered to have been normal. The patient was married at the age of 26 (1903) and widowed 12 years later. There were three pregnancies (1904, 1908, and 1911), all going to term. The menopause occurred about 1924 and was associated with the appearance of black spots before the eyes. Her general health up to the age of 37 (when the present illness began) was good, but there was some tendency to obesity. The past infectious illnesses include grippe (two attacks), and possibly measles and chicken pox. Although the patient is said to have suffered from "valvular disease" of the heart since about the time of onset of the present (physical) illness, there have been no definite symptoms of heart failure. A review of the organ systems discloses the following: chronic constipation, some tendency to gaseous eructations and "sour mouth", occasional mild swelling of the feet (probably postural or due to local lesions rather than cardiac), occasional frontal headaches, vague history of precordial pain about three years ago. There is no history of tuberculosis, syphilis, or gonorrhea.

Present Illness About 1913 (age approximately 37) the patient developed a psoriatic rash and at about the same time some form of multiple joint involvement

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that suggested at the time a questionable diagnosis of rheumatic fever. She remained in bed for about a year, during which time all her teeth gradually dropped out. The rash was early generalized, remained permanent and was refractive to treatment, however, it usually receded during the summer months of July and August. The joint involvement likewise persisted permanently, and it included the elbows, knees, and the articulations of the hands and feet. Deformities of the hands and feet appeared early in the course of the disease and progressed steadily, reaching in 1929 practically the extreme stage noted at the time of admission. Apart from the first year of illness, the patient was up and about, and active in caring for a large household until incapacitated by the psychosis.

General Physical Examination The patient was short, of pyknic habitus and despite the history of loss of weight, appeared well developed and nourished. Facial hirsuties and a tendency to prognathism were apparent, otherwise there were no signs related to possible endocrine stigmatization. A slight degree of exophthalmos (constitutional) was noted. The irides were discolored (old iritis), both eyes showed posterior synechiae, and the left eye was highly myopic with a posterior crescent. All the teeth were missing and the alveolar processes absorbed. The breasts were atrophic. The heart did not appear enlarged on percussion, the sounds were regular and of good quality, with accentuation of the second aortic sound and with a systolic murmur at the apical region. The radial artery was compressed with difficulty, and the blood pressure was 174 systolic and 100 diastolic. A second degree rectocele and external hemorrhoids were present. There was no evidence of trophic disturbances of the skin in the extremities and the dorsalis pedis was easily palpated in each foot. The neurological examination was negative; there was no motor weakness except that due to the bone and joint involvement, the deep reflexes were active and equal, and sensory changes in the extremities were not elicited.

Examination of the Skin There was a generalized psoriatic eruption with free coalescence of lesions and the production of many gyrate and polycyclic forms. The nails of the hands and feet were thickened, crusted and lined with prominent transverse grooves. The palms of the hands alone were spared in the generalized involvement.

Orthopedic Examination There was evidence of multiple joint involvement with the most striking changes in the distal portions of the extremities. The spine showed a moderate degree of kyphosis in the dorsal region and its motility was generally reduced.

Both shoulder joints appeared to be of normal size and permitted free movement except that on the right the patient could not raise the arm above the horizontal level and had to flex the elbow to reach overhead. The right elbow joint (figure 1) was enlarged and permitted extension only to about 120 degrees, the size of the left elbow joint and its movements were not remarkable. Pronation-supination of the forearm was considerably limited on the right but quite free on the left. There was complete ankylosis of the right wrist and partial of the left.

Both hands (figure 1) were deformed and shrunk to at least half their normal size, giving one the first impression of a congenital anomaly. The skin over the dorsum of the hand, particularly over the fingers, was loose, with the formation of transverse grooves most marked at the metacarpal-phalangeal joints. The interphalangeal joints showed complete ankylosis while the metacarpal-phalangeal articulations were transformed into ball and socket joints. There was practically no power in the fingers, the patient holding objects by pressure at the palms.

Motion was free and power good at the hip joints, which presented no superficial signs of abnormality. The right knee was slightly increased in size but permitted free motion, the left knee gave no positive findings. Movements of flexion-extension at both ankle joints were limited to within a range of about 10 degrees.

At both sub-astragaloid joints the movements of inversion-eversion were practically nil. The feet (figure 2) showed changes corresponding to those in the hands: considerable shortening at the metatarsal regions, marked shrinkage and deformity of the toes, complete ankylosis of the interphalangeal joints, transformation of the metatarsal-phalangeal joints into ball and socket articulations, and practically com-



FIG. 1

plete loss of power in movements of the toes. As a result of the deformities in the feet, the patient walked on the outside of the left foot and mostly on the heel of the right with a shuffling gait.



FIG 2

Laboratory Data Blood examination showed 3,700,000 red blood cells per cubic millimeter with 70 per cent hemoglobin (Sahli), and 7,500 white blood cells with a normal differential count.

Routine urine examination was negative except for the presence of 2 to 4 finely granular casts per low power field.

The blood Kahn test was negative. Examination of the spinal fluid gave normal results with regard to hydrodynamics, chemistry, cell count, and the Wassermann and colloidal gold tests.

Blood chemistry (January 14, 1934) showed the following

Serum total proteins 7.61 per cent
" albumin 4.11 per cent
" globulin 3.50 per cent
" calcium 8.74 per cent
" phosphorus 4.01 per cent

A hemolytic streptococcus agglutination test (November 24, 1935*) in which the patient's serum in dilutions ranging from 1:10 to 1:1280 was tested with a strain of hemolytic streptococci known to be agglutinated by arthritic serum in high dilution, was entirely negative.



FIG 3

Radiographic Report (Dr H. M. Wilson, Yale University School of Medicine) Films of both hands (figures 3 and 4) and the left foot (figures 5 and 6) made in this laboratory, and of the shoulders, knees and elbows made in another laboratory (Norwich State Hospital†) reveal the most striking changes in the extreme distal ends of the extremities with similar but milder changes in the more proximal portions of the extremities. There is some osteoporosis of all the bones, characterized by concentric atrophy with evidence of thinning of the cortical compact bone and associated with some coarsening of the trabeculations, which reaches an extreme degree in the

* This test was carried out in the bacteriological laboratory of the Hospital for Joint Diseases, New York City, through the courtesy of Dr H. L. Jaffe.

† The cooperation of Dr C. Waterman, Superintendent of the Norwich State Hospital, Conn., made possible the follow-up study of the patient and access to these films.

phalanges of the left hand The tendency to osteoporosis becomes accentuated about the joints, especially in the distal ends of the extremities, where massive absorption of bony substance occurs

There are osteochondritic changes in the shoulder joints most marked in the left shoulder about the humeral head characterized by irregular and alternating areas



FIG 4

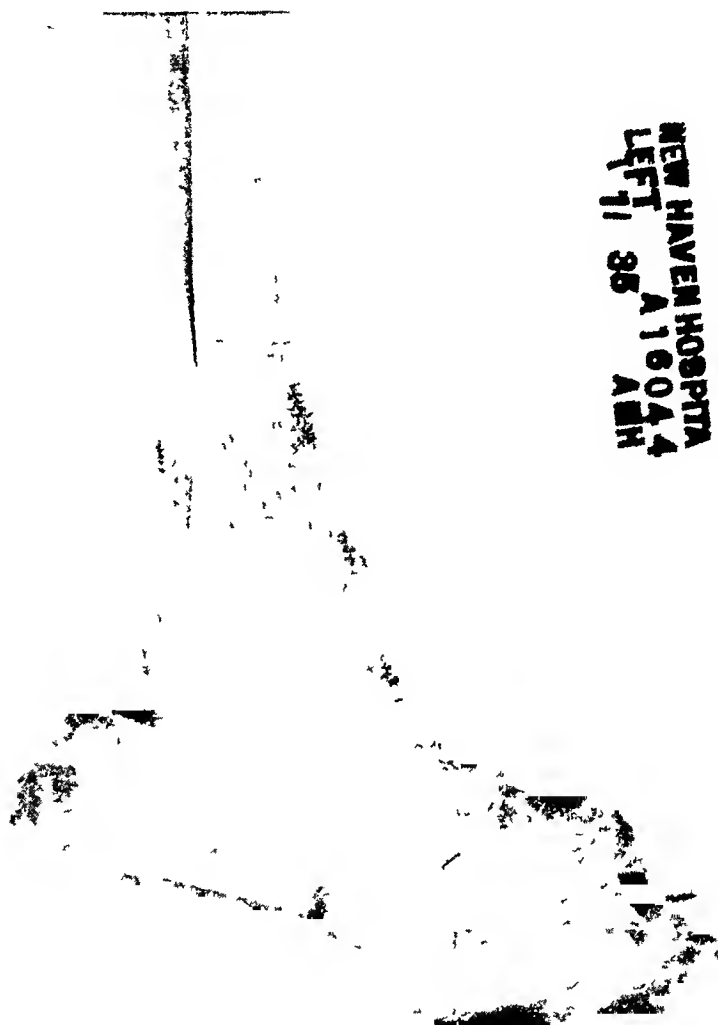
of rarefaction and condensation The right shoulder girdle shows a tapered narrowing of the outer end of the clavicle with loss of substance from its distal extremity The acromioclavicular joint space is widened There is condensation and irregularity of the acromion process

Moderate proliferative changes are noted in both knee joints, particularly about the superior aspects of the patellae This change appears to be associated with localized decalcification along the superior border at the attachment of the quadriceps tendon

The elbow joints show narrowed joint spaces with an irregular osteoporosis of the olecranon process giving it a spongy appearance There appears to be flattening and possibly telescoping of the radial head on the right

At the left hand the distal $2\frac{1}{2}$ centimeters of the left ulna are tapered to a point, with sclerosis and obliteration of the medullary cavity, the lower 3 centimeters of the left radius likewise show sclerosis and obliteration of the medullary cavity but without the tapered narrowing, and the articular surface is deformed The proximal carpal bones with the exception of the pisiform are missing while the distal carpal bones are fused into a contracted and flattened mass The carpo-metacarpal joint spaces are obliterated and the metacarpals show the same tapered narrowing with

loss of the heads which characterized the change in the left ulna. The proximal portions of the proximal phalanges show essentially the same changes as do the metacarpals. The distal portions of the proximal phalanges and the remaining phalanges show extreme osteoporosis with cortical outlines a fraction of a millimeter in width. As a result of the loss of bony substance of the lower ends of the radius



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FIG 5

and ulna, and of the carpals, metacarpals and phalanges, there is extreme shortening of the hand with the soft tissues creased and redundant. An essentially similar process involves the right hand although the changes are somewhat more pronounced in the hand and less marked in the carpus and radio-carpal joint than noted on the left.

The tarsals, metatarsals and phalanges of the left foot show a process similar to that involving the corresponding bones of the hand.

COMMENT

The clinical association of psoriasis and joint involvement, first comprehensively studied by Bourdillon (1888),¹ has been frequently described in the recent literature. Although practically every type of chronic joint disease has



FIG 6

been reported as occurring with psoriasis, one variety has received special emphasis with regard to its relationship to the skin condition. This form of arthritic disease is characterized by chronic usually multiple joint involvement often leading to early deformity and to gradual destruction of the joints. Some authors (Adrian,² Nobl and Remenovskiy,³ Zellner⁴), on the basis of certain clinical and roentgenological criteria, consider this type of arthritic disease peculiar to psori-

asis and would restrict the term "arthritis psoriatica" ("psoriasis arthropathica") to cases of psoriasis with this form of joint involvement. Others (Bauer and Vogl⁵), on the other hand, although admitting the existence of a probable etiological relationship between psoriasis and joint disease, deny the specificity of the articular changes of arthritis psoriatica and place them in the category of ordinary primary chronic (infectious) polyarthritis.

Whatever its nosological status, the group of cases included under the heading of arthritis psoriatica are characterized, as indicated above, by the frequent tendency to marked destructive changes of the joints. In some cases the destructive process also involves to a considerable degree the bone in the distal end of the extremities, resulting in a picture that would appear to be a mild form of the involvement characteristic of our case. Thus cases with atrophy and destruction of the phalanges of the hands and feet to the extent that several phalanges have been almost entirely absorbed are not uncommon (Adrian,² Wollenberg,⁶ Balzer and Burnier,⁷ Strom⁸, Schumacher and Lauter,⁹ Nobl and Remenovsky,³ Scholl,¹⁰ Rodnei¹¹). Extension of the destructive process to the metacarpals and carpals has also been observed if less frequently (Falk,¹ Zellner⁴). Furthermore in one case with metacarpal involvement (Zellner⁴) the distal ends of these bones have disappeared leaving tapering fragments of bone as seen in our case.

The involvement of the bone in the proximal portions of the extremities has not been described as frequently in arthritis psoriatica, but in a case reported by Lotze¹³ an area of rarefaction and condensation in the head of the humerus, and an area of absorption in the patella associated with proliferative changes in the knee joints resemble the lesions of the corresponding areas in our case.

In reviewing the literature we were able to find the description of only one case of psoriasis and bone and joint involvement which we would consider comparable to ours with regard to severity as well as to type of bone and joint change—that presented by Bauer and Vogl.⁵ In comparing the two cases one notes similar clinical courses and the same type of involvement of the hands and feet as characterized by the extensive loss of bony substance and the tapered narrowing of bony fragments. Bauer and Vogl consider their case an instance of ordinary primary chronic (infectious) polyarthritis, in keeping with their view referred to above, that cases of arthritis psoriatica fall into that category.

The bone and joint changes of our case also suggest a comparison with those described in a condition independent of psoriasis, namely, a rare form of arthritis, "main en lorgnette," only two cases of which have been reported in the literature—the original by Marie and Lévi,¹⁴ and the second by Weigeldt.¹⁵ These cases resemble ours in showing the following features: chronic progressive multiple joint involvement with extreme changes in the distal ends of the extremities, massive absorption of bone in the hands with tendency to tapered narrowing of bony fragments, and formation of transverse folds in the skin of the fingers (due to the disproportionate shrinkage of the bones and the soft tissues). This peculiar folding of the skin of the fingers, suggesting the appearance of an opera glass, prompted Marie and Lévi to select the descriptive name of "main en lorgnette." The two cases designated by this name are considered by their respective authors as special instances of chronic infectious polyarthritis.

The fact that a bone and joint process similar to that in our case appears in a condition not associated with psoriasis would argue against the assumption that

the type of bone and joint involvement characteristic of our case is peculiar to the skin condition, even if the two may be etiologically related

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CONGENITAL DILATATION OF THE PULMONARY ARTERIES REVEALED BY ROENTGENKYMOGRAPHY *

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ROENTGENKYMOGRAPHY is so new an addition to the diagnostic procedures of roentgenology that few physicians in general practice are aware of its value and diagnostic indications. The writer is of the opinion that the method has a wide field of usefulness and that it will come into general use in radiological practice as soon as its various applications are more generally known.

Roentgenkymography differs from other roentgenographic methods in that its single function is to record movement (and negatively, the absence of movement in organs or parts of the body that normally have movement). With this method it is possible to make a permanent graphic record of the movement of any part or organ of the body that can be depicted in the ordinary roentgenogram. Often the movement curves are susceptible of quantitative and qualitative analysis of great accuracy. Ventricular, auricular, and arterial movement curves are characteristic and show characteristic modifications in certain cardiovascular diseases. Movements of the diaphragm, gastrointestinal canal, deglutition, articulations, chest wall, etc., may be studied in the fixed curves of

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the kymogram, or the recorded cycle of movement may be reproduced visually in a special viewing machine, the kymetoscope which produces the illusion of continuous motion

The mechanical details and groundwork of roentgenkymography have been covered by Stumpf,¹ and Hirsch.² The next logical step is the reporting of specific cases in which the method has elucidated otherwise obscure points in the diagnostic picture. To justify itself, the method must give information that is not as readily obtainable by other methods. A first case of this kind was reported by the author in August 1935.³ The case reported herewith furnishes another illustration of the value of roentgenkymography in a type of case that usually presents diagnostic difficulties, congenital heart disease



FIG 1

CASE REPORT

The subject of this report is a white male school teacher, aged 38 years. He has no complaint and was unaware of his abnormality until he applied for life insurance in December 1934. His mother died in 1909, probably of tuberculosis. Aside from this, the family history is negative. He has been in good health prac-

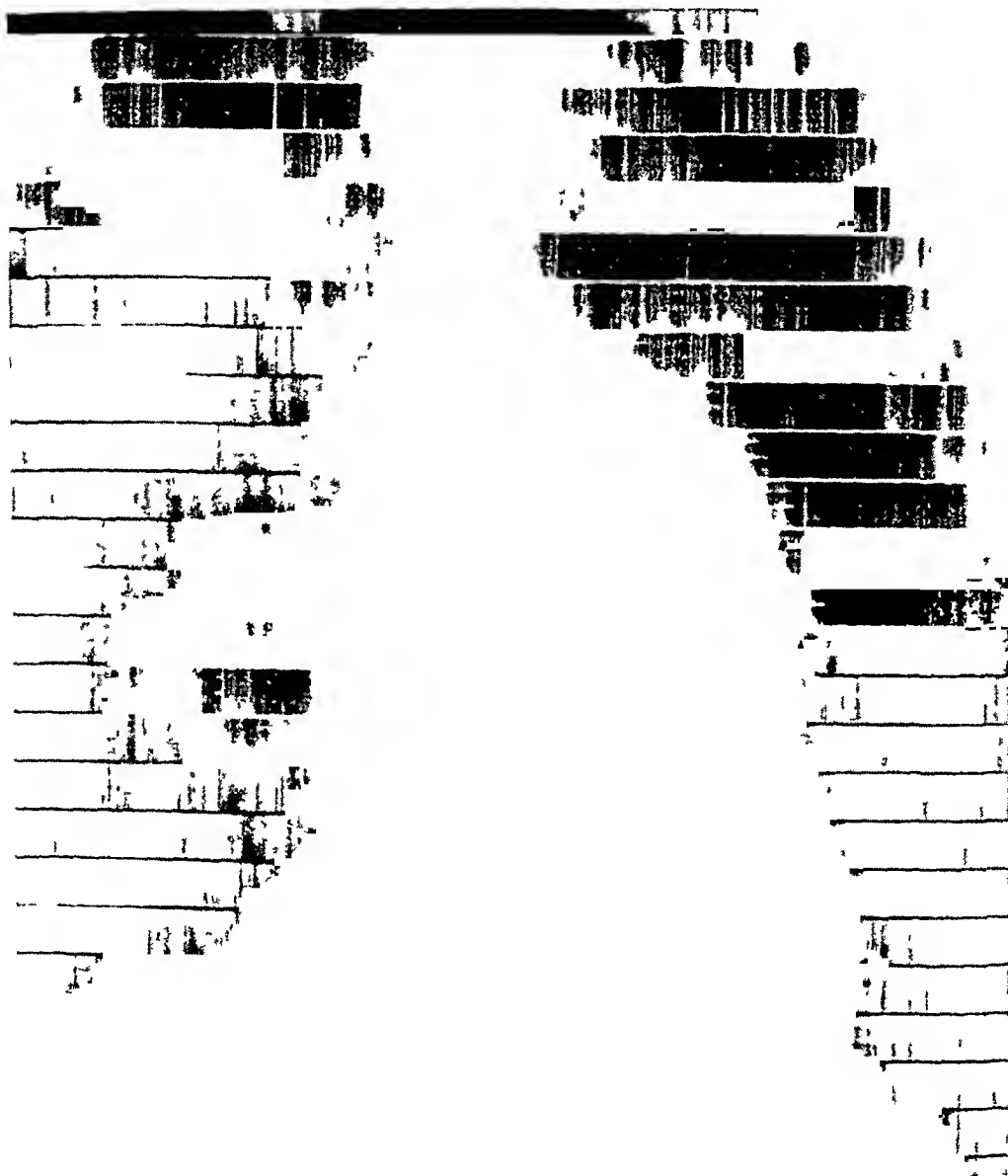


FIG 2

tically all of his life, but says that when he was a child his parents were told that he had an abnormal heart. He led a life of normal activity. There is no history of cough or expectoration. The man shows average build, development and nutrition. Pulse rate 84, blood pressure 104 systolic and 78 diastolic, respiratory rate 20, normal

temperature. He served in the World War and was discharged without disability. His tonsils were removed in 1929, and the appendix in 1930. In 1927 he had influenza and, due to a rather prolonged convalescence, visited a large clinic for general medical examination. He was told that he had mitral stenosis and would have about 20 per cent disability.

In 1934 an insurance company's medical examiner elicited percussion findings which led him to suspect old fibrotic tuberculosis and the applicant was referred to the Waverly Hills Tuberculosis Clinic. A chest film made at the Clinic (figure 1) shows large, sharply defined masses projecting into both lung fields, and pronounced enlargement of the upper left cardiac border. The lungs are singularly clear. No evidence of tuberculosis was found. The differential diagnosis lay between Hodgkin's disease or some other type of neoplasm and anomalies of the heart and great vessels. A faint presystolic murmur was the only abnormal heart sound elicited. There was no clubbing of the fingers. No subjective symptoms were present.

Because of the unusual roentgenographic findings, the patient was referred to the writer for roentgenkymographic examination with the idea of determining whether the masses in the thorax were of vascular origin or solid tumors. This question is clearly answered by the kymogram (figure 2). Not only do the masses show expansile pulsation, but the curves are unmistakably arterial.

In the light of these findings and of the history we believe that the evidence is sufficient to justify a diagnosis of congenital dilatation of the pulmonary arterial trunks and probably the ductus arteriosus and conus arteriosus. Conventional teaching would lead us to anticipate more in the way of physical signs and subjective symptoms in cases of this type. It seems probable that roentgenkymography will teach us some hitherto unknown facts about these cases, especially in relation to clinical manifestations.

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RAYNAUD'S DISEASE IN MAN

By A. M. RECHTMAN, M.D., F.A.C.S., *Philadelphia, Pennsylvania*

RAYNAUD'S disease in man is not common. Only seven cases were seen at the Mayo Clinic¹ which fulfilled the criteria Allen and Brown considered necessary for a diagnosis. It is generally conceded that the majority of male patients in whom a diagnosis of Raynaud's disease has been made have in reality been cases of thromboangitis obliterans.

Raynaud described four features whose presence he considered necessary for a diagnosis of the disease bearing his name:

- 1 Episodes of change in color, of the vasospastic type, excited by cold or emotion.

* Received for publication January 2, 1935.

- 2 Bilaterality
- 3 Presence of normal pulsations in the palpable arteries
- 4 Absence of gangrene or its limitation to minimal grades of cutaneous gangrene

To these Allen and Brown¹ added two further criteria

- 5 The absence of any disease which might be causal, such as organic disease of the nervous system
- 6 Symptoms of two years' or longer duration

The author feels that the following further requirements should be insisted upon in the interest of more accurate differential diagnosis

- 7 Obliterative vascular disease should be excluded, not only by the absence of gangrene (or its limitation to minimal cutaneous areas), but also by the determination of normal arterial pulsations by Pachon oscillometric readings, and by the demonstration of normal reflex temperature variations in the affected limbs with the thermocouple
- 8 The characteristic changes in the capillaries of the nailfold, described by Brown,^{2,3} should be shown to be present

Two male cases of peripheral vascular disturbance are presented which conform to the above criteria for Raynaud's disease. Both were studied on the author's orthopedic service at the Jewish Hospital in Philadelphia

CASE REPORTS

Case 1 M K, male, aged 36. The patient's symptoms started six (6) * years before his first visit on January 24, 1932. When his hands were exposed to cold weather, the second, third, fourth and fifth fingers became numb and "absolutely white" (1) The two distal phalanges of the second and third fingers, the distal phalanx of the fourth finger and the tip of the fifth finger of the right hand were involved. The numbness would abate when the patient was in a warm room for 30 minutes, or within five minutes if the hand was placed in hot water, when it then became red and dusky. Hyperesthesia as a pin- and needle-like sensation and a "scratchy, irritating, queer feeling" persisted until the normal appearance was restored. Placing the hands in cold water for five minutes caused the color changes. He learned to protect his hands against the cold which caused the syndrome and to warm them to hasten recovery.

On examination, January 30, 1932, at a room temperature of 70° F the color of both hands (2) was red and dusky, to above the wrists. The left or subjectively uninvolved side was more dusky. The face had the same color changes, but not the remainder of the body. Elevating the hands lessened the color, but not to the normal. The pulsations (3) were equal on both sides and of good volume in all the vessels of the upper extremities. The radial, and then the ulnar arteries were compressed, but no occlusion of the smaller vessels was demonstrated.

Pachon oscillometric (7) studies of the extremities showed the following readings

Right Arm	4	Left Arm	5
" Forearm	8	" Forearm	6
" Foot	2	" Foot	1
" Ankle	5	" Ankle	5
" Calf	10	" Calf	10

* The bold face numbers coincide with those of the criteria previously recorded as necessary for a diagnosis of Raynaud's disease

Thermocouple (7) readings (Coller and Maddock) were taken. The patient was exposed for an hour, the room temperature was 70 degrees. The average temperature on the right side was 28 degrees C and on the left side 28.5 degrees C. The body was wrapped in a rubber sheet, surrounded by blankets for an hour and the skin temperature readings were again determined. The right side averaged 32 degrees C and the left side 32.4 degrees C.

The systolic blood pressure was 106. There were no evidences of trophic changes in the nails (4) or of gangrene. The family history was negative for circulatory disturbances.

Roentgen-ray examination (5) showed no evidence of a cervical rib or other cervical bony lesion to account for the disturbed circulatory condition. Examination of the capillaries (8) of the nailfold* showed the findings to be similar in the fingers of either side (2). The capillaries in the field were shorter and fewer than usual. The capillaries were tortuous and slightly more dilated than normal.

Discussion This case fulfilled seven and partially the eighth criteria for a proved diagnosis of Raynaud's disease. The bilaterality was but partially fulfilled. The color syndrome with pallor was present in the right hand only. When no attack was present, the color of both hands was a dusky red. The capillary nailfold study showed findings on either side, similar to those seen in patients with Raynaud's disease.

Case 2 L. R. W., male, aged 22, was referred by Dr. A. E. Ohiensis. History: The patient first noticed the condition four years before his examination on May 5, 1933. He said the second finger of the left hand was blanched (white) on change of weather. The color changes occurred in cold or warm weather on damp or mucky days, and they also occurred when he put his hands in cold water (1). He first had a numb and stiff feeling, the part became white and then changed to a slightly reddish hue and felt warmer than normal. This continued for about 10 minutes. The color variation occurred at times when he was very tired, or if he washed his hands briskly. Two years after the onset, the third and fourth fingers were similarly involved. The precipitating factors remained the same. At times both hands were affected (2). During six months previous to this examination the left hand was only occasionally involved and only in very cold weather. The right hand was usually involved.

The patient said he made a bid of 420 of spades in a pinochle game and needed eight points to win. Toward the end of the playing he noticed that the second, third and fifth fingers of the right hand were blanched and white. The fifth finger was but rarely involved and had been involved only for the preceding year. The fifth finger was involved about one time in 50 episodes of change of color as compared with the second and third fingers of the right hand. The second finger on the left hand was involved about one time in ten.

The more frequent involvement of the right hand may have been due to its greater use in shaking hands (4), i.e. by pressure, or by its use in holding objects, such as a glass of ice water. The right hand alone was involved when the patient was excited, as during a card game. The stimulation of exposure to cold, however, caused both hands to be affected.

Examination The color of the patient's hands (1) changed from time to time during the several examinations made. The finger nails were all of a dusky hue. At times the color was normal. The color of the hands, to above the wrists, was usually dusky than normal. The color appeared normal when the hands were warmed beneath a blanket for an hour. At such times only were the hands warm.

*I wish to express thanks to Drs. Mitchell Rubin and C. H. Church of the staff of the Children's Hospital, Philadelphia, for their aid in the capillary nailfold studies.

The patient complained of a tingling sensation when the fingers were blanched. This continued during the period of cherry redness which followed. Blanching occurred on pressure of the hands, exposure to cold, and after excitement. It lasted for a period of from ten minutes to an hour and was of longer duration on a cold day. Blanching and stiffness first occurred in the second and third fingers and then in the fifth finger of the right hand. The color of the fingers changed to a dusky or purplish blue as the blanching abated. There was a sensation of numbness but no pain and the color gradually became a beefy red and a tingling sensation occurred. The natural color then returned but was a deeper red than normal unless the hands were warm. The normal color was slow in returning but it could be hastened by the application of heat or by massaging the fingers.

A study of the pulses (3) on palpation showed them to be equal in force and volume and present in all the palpable vessels of the extremities. Compression of the radial and then the ulnar arteries in both hands showed a normal return of the blood flow. The blood pressure was 114/80 on the left side and 112/82 on the right. Pachon (7) oscillometric readings were

Right Wrist	2	Left Wrist	1
“ Forearm	5	“ Forearm	4½
“ Arm	5	“ Arm	4½
“ Foot	½	“ Foot	+
“ Ankle	1¼	“ Ankle	1½
“ Calf	7	“ Calf	6
“ Thigh	6½	“ Thigh	6

Thermocouple (7) readings (Coller and Maddock) before dilation, at a room temperature of 72° F, showed the right hand averaged 23° C, and the left hand 23.4° C. After the patient was wrapped in a rubber sheet and surrounded with blankets for an hour the average skin temperature of the finger tips was 31.6° C on the right side and 32.3° C on the left side. There was no evidence of trophic, (4) gangrenous or ulcerative changes. Roentgen-ray examination for cervical rib was negative. A study of the capillaries (8) in the nailfold showed fewer capillaries to the field. The flow of blood in the capillary loops was slowed or stopped. The capillaries were more tortuous and had bulbous tips.

Discussion This case fulfills all eight criteria herein recorded for a diagnosis of Raynaud's disease.

SUMMARY

Two cases of Raynaud's disease in male patients are reported fulfilling the four criteria of Raynaud, and the two of Allen and Brown. These cases also met the additional diagnostic requirements suggested by the author, namely, normal oscillometric readings, normal reflex temperature variations, and characteristic abnormalities of the nailfold capillaries, in the affected extremities.

REFERENCES

- 1 ALLEN, E. V., and BROWN, G. E. Raynaud's disease affecting men, *ANN INT MED*, 1932, 1, 1384-1386.
- 2 BROWN, G. E. Personal communication, Dec 12, 1935.
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EDITORIAL

THE GASTRITIS PROBLEM †

IN the past decade there has been a marked revival of interest in gastritis. This is largely attributable to the following factors: (1) the present vogue, especially on the continent of Europe, of performing gastric resection for benign gastric and duodenal ulcers, as well as for malignant lesions, thus permitting histopathologic study of fairly large portions of the freshly resected gastric tissue, (2) the more general use of the gastroscope, which has been greatly improved in recent years, (3) progress in the roentgenographic study of the mucosal relief. Accessory to these major factors are the following: specialized biochemical and cytologic studies of the gastric secretion as an aid to the diagnosis of gastritis, researches directed to the experimental production of the lesion, investigations as to the rôle gastritis plays in the genesis of ulcer, carcinoma, various forms of anemia, and postoperative sequelae, accretions to knowledge from gastrophotographic observations, speculations concerning the clinical significance of gastritis when associated with duodenal or gastric ulcer, and finally, the influence of an increasing literature on the subject in the form of articles, monographs and atlases.

The problem of most concern to physicians and surgeons, simply stated, is this: To what extent is gastritis or gastro-enteritis, especially in its chronic form, the underlying cause of those conditions diagnosed as pseudo-ulcer, nervous indigestion, gastrototoxic hemorrhage, duodenitis, gastrogenic diarrhea, achylia gastrica, pseudocholecystitis, and of those relatively infrequent cases presenting antral defects, which are usually labeled scirrhus carcinoma or syphilis but which do not present evidence of either on histologic examination of the resected tissue? The same problem applies to certain late postoperative sequelae. What diagnostic procedure is the most reliable? Granting the presence of gastritis, to what extent is that condition responsible for the underlying complaint in a given case?

With certain primary and secondary types of gastritis—acute, subacute, chronic phlegmonous, specific and perianastomotic—we have long been familiar. The acute and chronic forms of alcoholic gastritis, atrophic gastritis associated with pernicious anemia, and the phlegmonous form of gastritis have been particularly well known. The hypertrophic, subacute and chronic forms have been frequently found at necropsy to be associated with disease of the liver, heart, gall-bladder and certain metabolic and endocrine disorders. Syphilitic gastritis in its various forms has been encountered repeatedly. In more recent years we have become impressed with the frequency of occurrence of hypertrophic, erosive and ulcerative forms of subacute gastritis in association with obstructive lesions of the stomach and duodenum. Baker's recent histopathologic studies of the

* Submitted for publication July 30, 1936

gastric mucous membrane of patients undergoing gastric resection for malignant and benign lesions, with or without obstruction, also discloses the high frequency of occurrence of definite gastritis even in gastric mucous membrane remote from the lesion. This fact does not necessarily imply that gastritis was a precursor of the ulcer or cancer.

Of especial interest are those instances of primary gastritis encountered at operation and confirmed by histologic examination of excised or resected gastric tissue. In such cases the inflammatory process is sufficiently extensive to give rise to gross defects, usually antral in situation and recognizable by the ordinary roentgenologic technic. Such defects are indistinguishable from those produced by carcinoma in particular, by syphilis, by chronic hypertrophy of the pylorus, and by gastric ulcer when associated with antral spasm. From a symptomatic standpoint the cases can roughly be divided into three types according as to whether they simulate (1) cases of ulcer or cancer with irregular symptoms, (2) cases in which the symptoms closely simulate those of ulcer, and (3) cases characterized by pain, or simulating cholecystic disease.

From the symptomatic standpoint, the traditional conception of gastritis, of the subacute and chronic variety in particular, in contrast to the contemporary conception, is worthy of consideration. Past teaching and experience led to the belief that changes confined to the gastric mucosa did not necessarily give rise to any frank gastric phenomena, with the exception of occasional hemorrhage and possibly of vague epigastric discomfort, although such indirect symptoms as anemia and intestinal disturbances, especially diarrhea, frequently occurred. But such authorities as Faber, Schindler, Henning, Konjetzny, Katsch and others, on the basis of gastroscopic, surgical and pathologic findings maintain that a variety of symptoms common to gross lesions of the stomach may be engendered by the various forms of gastritis. While it is still true that extensive gastritis may be present without giving rise to any appreciable gastric disturbances, increasing experience justifies the pronouncement of the authorities just cited. Certainly, primary subacute and chronic, erosive and ulcerative forms of gastritis, in which the gastric content contains free hydrochloric acid, do give rise to symptoms highly suggestive of gastroduodenal ulcer or to massive hemorrhage, and the chronic hypertrophic anacid variety may engender less active symptoms suggestive of cancer, cholecystic disease, or functional gastric disorders as well as of ulcer.

Of all the procedures advanced for the diagnosis of gastritis, it is generally conceded that gastroscopy is the most reliable. Careful roentgenoscopic study of the mucosal relief is helpful at times. In Berg's opinion, characteristic of gastritis from the roentgenologic standpoint, is the elevation, swelling, coarseness and stiffness of the mucosal fold, the product of inflammation. The atrophic, erosive, and superficial ulcerative forms are usually difficult of detection. An inflammatory condition following gastroenterostomy may be indicated by swelling of the folds in the stomach and

efferent loop, and the roentgenologic diagnosis of gastrojejunitis, in experienced hands, is usually reliable. Apparently the most reliable roentgenoscopic evidence is that in which the inflammatory process was sufficiently extensive to give rise to gross defects. The question naturally arises as to how often gastric disturbances are the result of patchy or diffuse inflammatory states unrecognized in the absence of roentgenographic findings and in the absence of routine gastroscopic study. The gastroscopic appearance of the stomach in various forms of gastritis is instructively portrayed in the monographs or atlases of Schindler, Henning, and Moutier.

It is unfortunate that gastroscopy is such a highly technical procedure. In unskilled hands it is also a dangerous one. The circumspect physician cannot escape the conviction at times that some pathologists, gastroscopists and even roentgenologists or other protagonists of gastritis as an important entity, are unduly imbued with an enthusiasm comparable to that displayed on occasions by certain allergists and endocrinologists. One also gets the impression that the enthusiastic gastroscopist finds some abnormality of the gastric mucosa, to which he attaches undue significance, in the majority of cases in which he makes an examination. In this respect Katsch himself has pointed out the fallacy of a diagnosis made exclusively from the results of gastroscopic examination because, "a clear relation between gastroscopic findings and the clinical picture, even excluding everything but the subjective illness, can be established only in clear-cut cases with any degree of certainty."

The necessity for careful appraisal of all the facts, subjective and objective, as in other phases of medicine, is obvious. Careful teamwork among clinician, laboratory worker and surgeon is often essential in order that diagnostic and therapeutic problems in this field may be successfully surmounted.

G E

REVIEWS

The Normal Diet and Healthful Living By W W SANSUM, R A HARE, and R BOWDLN 243 pages, 12 × 22 cm Macmillan Company, New York 1936 Price, \$2 00

This is a book intended for popular appeal, written by the authors to present in a permanent form, especially for their own patients, facts of general health interest. A bird's eye view is given of such topics as the elements of nutrition, the vitamins, the physiology of digestion, the "elimination of wastes," and many familiar medical disorders including indigestion, allergy, underweight and overweight and the care of teeth. Finally, there is a brief discussion of bacteriology, especially as it relates to focal infection, with particular emphasis upon the work of Dr E C Rosenow. The material which has been mentioned occupies the first 186 pages of the book. The remainder is taken up with the customary appendices to be found in such treatises, including a few words on menu planning, followed by the usual sample menus, food tables, and weight tables.

G A H

A Textbook of Obstetrics for Students and Practitioners By FRIDRICK C IRVING, A B, M D, F A C S 558 pages, 24 × 15.5 cm Macmillan Company, New York 1936 Price, \$6 00

Good textbooks on obstetrics are always timely. By sound conservative advice they advance the efforts of the profession to reduce maternal mortality.

In elaborating the outlines used in the teaching of students in the Harvard Medical School, the author has created a clear and useful textbook. In keeping with the avowed purpose of making the book concise, the author has intentionally avoided the history of obstetrics, and the presentation of all sides of controversial subjects, and frankly states that the work does not cover the entire field. The contents are discussed under the conventional headings, and the index is ample. With the exception of the roentgenogram reproductions, which for the most part are only fair examples of the subjects which they are intended to illustrate, all of the 357 illustrations are clear outline drawings many of which have been modified from other works to which due credit is given. Attention is called to the excellent bibliography to be found at the end of each chapter which should prove invaluable to students and practitioners using this book as a guide. The pathologic descriptions are thorough.

The author prefers pentobarbital and scopolamine as analgesic agents during labor and uses rectal ether to control excitement. The toxemias of late pregnancy are classified as preeclampsia and eclampsia. Gynoplastic repairs following delivery are definitely frowned upon as is also the so-called "prophylactic forceps" operation. One cannot but feel that the descriptions of operative procedures are given too much space, and that prenatal and postnatal care should be given more emphasis in any work intended for the student and practitioner.

The author states that the book represents the policies and practice of the Boston Lying-In Hospital, and from it we learn that such obstetrical complications as septic abortion, placenta previa, premature separation of the normally implanted placenta, and eclampsia are treated conservatively in that clinic. Of especial interest to the readers of this journal are the discussions of the medical complications of pregnancy. These are brief but give concisely the author's viewpoint as an obstetrician on such questions as the indications for the termination of pregnancy.

The book is well written, and since it presents the author's vast experience in obstetrics in a readable form, it should prove of definite value to the student and practitioner to whom it is warmly recommended

J E S

The Bacteriology of Typhoid Salmonella and Dysentery Infections and Carrier States BY LEON C HAVINS, M D, Director of Laboratories, Alabama State Department of Health First Edition 158 pages The Commonwealth Fund, 41 East 57th St, New York City

This small volume sums up certain investigations and experiences of the author while actively engaged in public health work in the field and laboratory In thirteen short chapters, each with its summary and bibliography, the more important characteristics of the intestinal bacteria are discussed and selected laboratory methods described Clinical bacteriologists will find the book of especial interest A sense of undue brevity and of incompleteness in some of the chapters may be explained by the fact that the work was posthumously published

S L J

Examination of the Patient and Symptomatic Diagnosis JOHN WATTS MURRAY M D Second Edition 1219 pages C V Mosby Co, St Louis 1936 Price, \$10 00

This work is an effort to present, in minute detail the procedure for obtaining a clinical history and performing a physical examination The book is divided into two sections, the first on history taking and general physical examination, the second on specific symptoms and physical signs of disease localized in organs or body parts

After a long introduction, the author presents an outline of history and physical examination, then proceeds to an extremely minute analysis of history taking, given in catechism, or question and answer form The answers are frequently cast in the shape of lists of diseases which may be related to certain conditions, an unfortunate method, since the lists are so long as to make this section almost unreadable

Many statements are introduced as facts which do not bear up under analysis For example, in the section on Past History, question five—"Has the patient ever had diabetes?"—is answered thus, "Pulmonary tuberculosis is perhaps the most frequent complication in consequence of diabetes, the diabetic state following its development"

Question eight "Patient ever had chlorosis or anaemia?" Answer "Chlorosis may give rise to gastric ulcer, exophthalmic goiter, amenorrhea" On Page 68 "Cardiac hypertrophy, cardiac valvular disease, atheromatous degeneration of the arteries, and aneurysm may cause hemorrhagic neuroretinitis" Page 70 "Floating kidney may cause dilatation of the stomach" These, and many other similar statements, are offered without explanation or qualification

In the second section diseases of specific parts or tracts of the body are considered Each division is preceded by some details of history and physical examination, again in question and answer form, with the answers suggesting the disease possibilities The reader is evidently expected to refer to the paragraphs describing those diseases, although specific references are not given Many of the disease descriptions are very good, especially those of the respiratory tract On the other hand, several very important ones are apparently missing entirely The index, for example, does not list lobar pneumonia, typhoid fever, or pernicious anemia, although these diseases are mentioned at times in the text

The reviewer doubts if this book could be of much help unless it were used simply as an aid to other texts Many suggestions in it are very helpful, but as a whole, it would be improved by condensation and rearrangement

T N C

Collected Writings of ALFRED F HESS with biographical memoir and bibliography
2 volumes, cloth, 1453 pages, illustrated Charles C Thomas, Baltimore 1936
Price, \$15 00

The more important scientific contributions of Alfred Fabian Hess have been collected, edited and published in two well bound, well printed volumes. Abraham Flexner wrote an appreciative and interesting biographical memoir which precedes the writings. In this sketch are traced the main events of Hess' life and the principle influences which shaped it. It contains as well a critical appraisal of his work as a scientist and investigator and the place he holds in pediatrics.

The collected papers represent some of the most important investigative work done in medicine during the first third of this century. Such broad topics as tuberculosis in infancy, the antiscorbutic vitamin and infantile scurvy, and the effect of irradiation of foodstuffs are discussed in the reports of numerous investigations. One is impressed at how much pioneer work this man did and how many accepted and well trod avenues of medical thought were either indicated or opened up by his researches. In addition to the above mentioned investigations there are papers on rickets, purpura, alimentary intoxication and various other pediatric problems. It is characteristic of these articles that they are short, well written and easy to understand. His complete bibliography is appended to the work.

In summing up Hess' position Dr. Edwards A. Park writes, "Dr. Hess was the foremost investigator among pediatricians in this country." "A great skirmisher on the forefront of scientific progress, with an almost uncanny eye for the point at which the next attack should be made, with a genius for predicting the course which investigation should take, with almost infallible judgment on the basis of slight evidence and simple experiment as to where the weak point in the armor of ignorance lay." "Hess was the best example of what can be accomplished in science by the ability to think alone and unaided."

These volumes are a valuable addition to the library of any one interested in medical and pediatric progress.

T C G

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the following gifts received recently for the Library of the American College of Physicians from the authors

- Dr Percy Brown (Fellow), Boston, Mass—1 autographed book, "American Martyrs to Science Through the Roentgen-Rays",
- Dr George B Eusternian (Fellow), Rochester, Minn—1 autographed book (with Dr Donald C Balfour), "The Stomach and Duodenum",
- Dr Frederick T Lord (Fellow), Boston, Mass—1 autographed book, "Lobar Pneumonia and Serum Therapy",
- Dr Herman O Mosenthal (Fellow), New York, N Y—1 autographed book, "The Diagnosis and Treatment of Variations in Blood Pressure and Nephritis",
- Dr William M LeFevre (Fellow), Muskegon, Mich—2 reprints,
- Dr Lewis J Moorman (Fellow), Oklahoma City, Okla—3 reprints,
- Dr Joseph M Perret (Fellow), New Orleans, La—13 reprints,
- Dr Maxim Pollak (Fellow), Peoria, Ill—1 reprint,
- Dr William B Rawls (Fellow), New York, N Y—3 reprints,
- Dr Martin J Synnott (Fellow), Deceased—1 reprint,
- Capt Elbert DeCoursey (Associate), M C, U S A—1 reprint,
- Dr Harold R Keeler (Associate), Philadelphia, Pa—5 reprints,
- Dr Arthur R Masten (Associate), Wheat Ridge, Colo—5 reprints

Dr Edward L Turner (Fellow), from 1931 to 1936 associate professor and professor of internal medicine, American University of Beirut, Beirut, Syria, has recently accepted the appointment of professor of medicine and head of the division of medicine at Meharry Medical College, Nashville, Tenn. He will spend his full-time with the work of the college and hospital in connection with the reorganization of the division of medicine

Dr Ralph M Fellows (Fellow), for sometime connected with the Menninger Clinic at Topeka, Kan, has accepted the superintendency of the Osawatomie State Hospital, Osawatomie, Kan

The Washington Society of Pathologists has elected the following officers for the coming year: Dr Roger M Choisser (Fellow), President, Capt Elbert DeCoursey (Associate), M C, U S A, Secretary-Treasurer

Dr Matthew Shapiro (Associate), New York City, has been appointed assistant professor of clinical medicine in Columbia University College of Physicians and Surgeons

Dr R H Kampmeier (Fellow), has left Louisiana State University Medical Center to accept an appointment at Vanderbilt University School of Medicine, Nashville, Tenn

Dr George A Gray (Associate), formerly of Abilene, Tex., has become Director of the Nolan County Health Unit, Sweetwater, Tex.

Dr John H Musser (Fellow), New Orleans, La., was the guest clinician on the program of the Post-Graduate Assembly of the North Carolina State Medical Society at Banner Elk, N C., August 20 to 21. The Post-Graduate Assembly is conducted on "Internal Medicine and Therapeutics."

The Committee on Arrangements included Dr R H Hardin (Fellow), Banner Elk, N C., Chairman, Dr C L Sherrill (Fellow), Statesville, N C., and Dr James W Vernon (Fellow), Morganton, N C.

Dr Wingate M Johnson (Fellow), Winston-Salem, N C., President-Elect of the North Carolina State Medical Society, delivered an address on "My Experience with Influenza", Dr Verne S Caviness (Fellow), Raleigh, N C., "Pneumonia", Dr C H Cocke (Fellow), Asheville, N C., Governor for North Carolina and Chairman of the Board of Governors, "Evolution of the Modern Treatment of Tuberculosis", Dr D W Holt (Fellow), Greensboro, N C., "Backache". Dr L B McBrayer (Fellow), Southern Pines, N C., Secretary and Treasurer of the North Carolina Medical Society, and also Dr Musser presented addresses on the evening of the banquet.

Dr George R Minot (Fellow) and Dr C Sidney Burwell (Fellow), Dean of Harvard Medical School, were among those who addressed the Boylston Medical Society, on the occasion of its one hundred and twenty-fifth anniversary recently. The Boylston Medical Society is probably the oldest students' medical school organization in America. The dinner was held at the Harvard Club. Dr Burwell is President-Elect of the Society.

Dr William G Herrman (Fellow), Asbury Park, N J., has been advanced from 1st Vice-President to President-Elect of the Medical Society of New Jersey. Dr Francis R Haussling of Newark, who was installed as President, resigned because of ill health, whereupon Dr Spencer T Snedecor of Hackensack, President-Elect, was advanced to the Presidency and Dr Herrman to the post of President-Elect.

Dr Warren Coleman (Fellow), New York City, is one of the Vice-Presidents of the Physicians' Home, which has been recently reorganized and which now plans a vigorous campaign to finance a permanent home for aged and infirm physicians.

Dr Guy C Jarratt (Associate), Vicksburg, Miss., has been reelected Secretary of the Mississippi State Pediatric Society.

Dr J Arthur Myers (Fellow), Minneapolis, Minn., and Dr Samuel H Snider (Fellow), Kansas City, Mo., are Vice-Presidents of the newly formed American Academy of Tuberculosis Physicians.

Dr Andrew C Ivy (Fellow), Chicago, has been elected Vice-President of the Chicago Society of Internal Medicine.

Dr Mark S Knapp (Fellow), Ann Arbor, Mich, has announced his resignation as executive secretary and director of medical research of the Rackham Fund, Detroit, a position he has held since the fund was created in 1934

Dr John D Dunham (Fellow), Columbus, Ohio, has been appointed to the city board of health, succeeding the late Dr Wells Teachnor, Sr

Dr Charles E Sears (Fellow), Portland, Ore, has been made President-Elect of the Pacific Northwest Medical Association

Dr Clayton E Royce (Fellow), Jacksonville, Fla, has been elected a Vice-President of the Chattahoochee Valley Medical Association

Dr Anthony Bassler (Fellow), New York City, and Dr Martin E Rehfuss (Fellow), Philadelphia, have been appointed President and Vice-President, respectively, of the American delegation to the International Congress on Hepatic Insufficiency in Vichy, France, September 16 to 18, 1937

Dr Newton G Evans (Fellow) is President of the Los Angeles Cancer Society

The pathology laboratory of Beth Israel Hospital has been dedicated in honor of Dr Isidore W Held, clinical professor of medicine at New York University College of Medicine, the dedication ceremonies taking place on Dr Held's sixtieth birthday. Among speakers at the dedication was Dr John Wyckoff (Fellow), dean of New York University College of Medicine

The sixty-sixth annual session of the Colorado State Medical Society was held at Glenwood Springs, September 9 to 12. Aside from the regular program, there was a presentation of the past presidents of the Society, in the order of their seniority. Dr Hubert Work (Fellow), Englewood, Colo, former President of the American Medical Association and Secretary of the Interior under President Coolidge, was presented as the senior living president of the Society. The banquet was dedicated to Dr Josiah N Hall (Fellow), Denver, for several years the Colorado Governor for the American College of Physicians, in recognition of his fiftieth year of attendance at the annual meetings of the Society. Dr Hall has been a member of the Society fifty-two years. He has been a president of the State Society, of the State Board of Health and of the State Board of Medical Examiners. He has served on the Judicial Council of the American Medical Association and has been a member of the House of Delegates at various times. Dr Hall has been professor of medicine at the University of Colorado School of Medicine for many years.

Dr Guy H Turrell (Fellow), Smithtown Branch, N Y, is Secretary of the New York State Sanitary Officers' Association, the name of which has recently been changed to the New York Health Officers' Association

Dr Wade W Oliver (Fellow), professor of bacteriology, Long Island College of Medicine, Brooklyn, has been elected Secretary of Health Research, Inc, a non-profit corporation recently formed by the New York City Department of Health to accept and administer funds offered for financing research in the city's laboratories. The department plans to open a convalescent serum center

Dr Henry M Moses (Fellow), Brooklyn, is the director of the medical service of the new Brooklyn Cancer Institute, opened at Kings County Hospital during September, as an independent clinical unit of the division of cancer of the city department of hospitals. Surgical and radiotherapy services under individual directors have also been established. The three directors will be responsible for clinical policy in general and for the treatment and care of patients individually. The institute is under the general administrative supervision of the medical superintendent of Kings County Hospital. There is a visiting staff of thirty-one physicians. Beds are to be used as far as possible for cases of doubtful classification and for recognized tumor cases requiring short hospitalization, in order that the patients still reclaimable may find facilities for care

Dr William V Wilkerson (Fellow), Highcoal, W Va, is president of the Boone County (W Va) Medical Society

Dr Daniel L Finucane (Associate), formerly of Glenn Dale, Md, has been appointed associate professor of clinical medicine at Georgetown University School of Medicine, Washington, D C

Dr J P Bowdoin (Fellow), Atlanta, Ga, has been elected Secretary-Treasurer of the Georgia State Child Health and Welfare Council

Dr Leon S Lippincott (Fellow), Vicksburg, Miss, has been elected Secretary-Treasurer of the Mississippi State Hospital Association, Dr Lippincott is also Secretary of the Mississippi State Charity Hospital at Vicksburg

Dr Franklin B Bogart (Fellow), Chattanooga, Tenn, has been elected Secretary-Treasurer of the Tennessee Radiological Society

The Texas State Heart Association has elected the following officers for the coming year: Dr Edward H Schwab (Fellow), Galveston, President, Dr George R Herrmann (Fellow), Galveston, Vice-President, Dr Robert M Barton (Fellow), Dallas, Secretary

Dr John G Young (Fellow), Dallas, Tex, is Vice-President of the Texas Pediatric Society for the coming year

Dr Walter B Martin (Fellow) and Dr Frank H Redwood (Fellow), both of Norfolk, have been elected President and President-Elect, respectively, of the Norfolk County (Va) Medical Society for the coming year

Dr Frank C Hodges (Fellow), Huntington, W Va , has been elected a Vice-President of the West Virginia State Medical Association

Under the Presidency of Dr David Riesman (Fellow), Philadelphia, the Interstate Postgraduate Medical Association of North America is holding its International Assembly for 1936 at St Paul, October 12 to 16

Dr W A Dearman (Fellow), formerly of Gulfport, Miss , has been appointed assistant superintendent of the Mississippi State Hospital at Whitfield

Dr W M Sheppe (Fellow), Wheeling, W Va , has been elected Secretary of the Ohio County (W Va) Medical Society for the coming year

Dr Martin E Rehfuss (Fellow), Philadelphia, clinical professor of medicine at Jefferson Medical College of Philadelphia since 1933, has been promoted to professor of clinical medicine



With warmest regards of your friend
J. H. Stuckey
November 29th 127.

OBITUARIES

DR JAMES MESCHTER ANDERS

James Meschter Anders, M D , Ph D , LL D , Sc D , the Nestor of Philadelphia's medical profession, the first Master of the American College of Physicians and its President during 1922-23, died at his summer home at Bluehill Falls, Maine, on August 29, 1936, aged 82

Dr Anders was born in Fairview Village, Montgomery County, Pa , on July 22, 1854, and received his education in the public schools of Norristown, Pa , and at the theological seminary, under the auspices of the Mennonite Church, at Wadsworth, Ohio In 1877, he graduated from the University of Pennsylvania School of Medicine and in the same year received his degree of Doctor of Philosophy

He served his internship at the Episcopal Hospital, Philadelphia, and, in 1888, became visiting physician to the same institution One year later Dr Anders was appointed visiting physician to the Medico-Chirurgical Hospital and in the same year was made a member of the visiting staff of the Philadelphia General Hospital

In 1889, Dr Anders became a lecturer on *Materia Medica* at the Medico-Chirurgical College, and one year later was elected Professor of Hygiene and Pediatrics In 1891, Dr Anders became Professor of the Theory and Practice of Medicine and Clinical Medicine in the Medico-Chirurgical College, a position he held with credit and honor for over twenty-five years Dr Anders was the author of a textbook known as the "Principles and Practice of Medicine," which passed through fourteen editions, and he was co-author of a "Text Book of Medical Diagnosis "

Dr Anders was a frequent contributor to medical literature throughout his long and distinguished career, over a hundred scientific articles being listed from his pen He was widely and favorably known as a conservative and helpful consultant by the medical profession, and his services were sought by practitioners, both at home and at distant points

Dr Anders was greatly interested in educational and civic problems afieid from medicine and, at the time of life when many physicians become both formalized and even crystalized in thought, possessed a clarity and breadth of vision inspiring to all who were fortunate enough to come into contact with him

Dr Anders was much interested in Preventive Medicine and advanced its interests by practical application of sound principles as well as by well thought out addresses before influential professional and lay groups

In 1923, he was made a Chevalier of the Legion of Honor of France and, in 1928, had the honorary degree of Sc D conferred upon him by his Alma Mater, the University of Pennsylvania Many other well deserved honors, medical, civic and national, were bestowed upon Dr Anders, but he

remained, as in the beginning, modest, unselfish, altruistic, and was possessed by an admirable desire to prove useful to his profession, his patients and to the general public weal

The American College of Physicians was very dear to the heart of Dr Anders and he devoted much time and thought to how this organization could best advance and uphold the interests of the medical profession and the public the profession serves

Dr Anders' death has caused the College to lose a much admired and beloved Master, the medical profession a skilled and devoted practitioner, and the world has lost a man of exemplary character who spent his long life in attempting to make the problems of others less difficult

E J G BEARDSLEY M D , F A C P ,
Governor for Eastern Pennsylvania

DR EDWARD GILMER THOMPSON

Dr Edward Gilmer Thompson (Fellow), Memphis Tennessee, died June 21, 1936, aged 52 years

Dr Thompson was born in Louisa, Virginia, August 29, 1884, and in his early years his family moved to Marianna, Arkansas, where he resided until he came to practice his profession in Memphis in 1913

He secured his preliminary education in the public schools of Marianna and later attended the Branham and Hughes Preparatory School. He received the degree of Bachelor of Arts at Vanderbilt University in 1907 and his medical education was obtained at the University of Pennsylvania from which he graduated with honors in 1911. He was a member of the Phi Delta Theta, Alpha Kappa Kappa and Alpha Omega Fraternities

Following his graduation in medicine he served a two year internship at the Episcopal Hospital in Philadelphia, Pennsylvania, and in 1913 began the practice of medicine in Memphis, Tennessee. He devoted his professional career to internal medicine, was a Fellow of the American College of Physicians and Associate Professor of Medicine at the University of Tennessee College of Medicine, held staff positions at the Methodist and John Gaston Memorial Hospitals and was on the staff of the Illinois Central Railway System

In 1917 he was among the first to offer his services to his country in the great war. With the rank of Captain in the Medical Corps he was a member of Hospital Unit P and for fourteen months was attached to Base Hospital 15 at Chaumont, France. Though quiet and unobtrusive Dr Thompson took an active interest in organized medicine, being a member of the Memphis and Shelby County Medical Societies, Tennessee State Medical Association, The American Medical Association and the Southern Medical Association

Edward Thompson was not only much beloved by a large clientele but he was a doctor's doctor, being the personal physician probably of more of

the Memphis medical profession than any other member of it. His strong sense of fidelity to his patients doubtless shortened his life. His personal traits of character were outstanding. Clean in word and thought and deed, faithful, conscientious and loyal to his high conception of his duty, no one ever heard a harsh or unkind word spoken of him. He was loved and deservedly trusted implicitly by everyone who knew him. Competent, dependable, wholly trustworthy, the profession in Tennessee can ill afford to lose him.

J. OWSLEY MANIER, M.D., F.A.C.P.,
Governor for Tennessee

DR. JAMES FRANKLIN ACKERMAN

Dr. James Franklin Ackerman (Fellow), Asbury Park, N. J., one of six sons of Joseph and Susan Ackerman, was born in Nashua, N. H., December 29, 1864. He received his preliminary education at Francestown Academy in New Hampshire and in the public schools of Shelburn Falls, Mass. He received a portion of his college training at Amherst College, followed by his medical training at the New York Homeopathic College, New York City, graduating in 1890. Thereafter he immediately went to Asbury Park, where he resided until his death on August 5, 1936. He was associated with his late brother, Dr. Joseph Ackerman, who died about a year ago.

Dr. Ackerman was highly regarded as a citizen in Asbury Park and was affectionately referred to as the "father" of two different hospitals, and at the time of his death was chief of staff of the Ann May Hospital, Spring Lake, and of the Fitkin Memorial Hospital, Neptune, which succeeded it. He was ex-president of the Asbury Park Medical Society, the Monmouth County Medical Society and the New Jersey State Homeopathic Society. He was an active member of the New Jersey State Medical Society, the New York Academy of Medicine and the American Medical Association. He had been a Fellow of the American College of Physicians since 1931.

Dr. Ackerman is survived by his second wife, Mrs. Anna Rouse Ackerman, a brother, George, of Nashua, N. H., and three daughters, Mrs. James A. Fisher, Mrs. Frank W. Cole and Miss O. K. Parry, all of Asbury Park.

Both the College and the medical profession have suffered a great loss in the death of this valuable member.

CLARENCE L. ANDREWS, M.D., F.A.C.P.,
Governor for New Jersey

DR. SIDNEY KOHN SIMON

"Sidney Kohn Simon, born, New Orleans, La., January 25, 1878, A.B., 1899, Tulane University College of Arts and Sciences, M.D., 1903, Tulane

University of Louisiana Medical Department, visiting physician, 1905-12, Charity Hospital, New Orleans, visiting physician, 1905 to date, and chief of Gastro-Intestinal Department, 1920 to date, Touro Infirmary, professor of gastro-enterology, Tulane University of Louisiana School of Medicine, member and ex-member of council, American Gastro-Enterological Association, member and ex-president, Southern Gastro-Enterological Association, ex-secretary and ex-member of council, American Society of Tropical Medicine, ex-secretary and ex-chairman of the Section on Gastro-Enterology, and Fellow, American Medical Association, member, Southern Medical Association and Southern Gastro-Enterological Club, Fellow of the American College of Physicians since 1928 "

Dr Simon has for years been regarded as an outstanding leader in his chosen specialty, gastro-enterology

His contributions to the literature of this field of medicine have been too numerous to mention at this time Suffice it to say that the influence of his writing and clinical teaching constitutes a living and lasting monument to his memory in the minds and hearts of the medical profession

J E KNIGHTON, M D , F A C P ,

Governor for Louisiana

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THE POSTURAL SYNDROME RELATED TO OBESITY LEADING TO POSTURAL EMPHYSEMA AND CARDIORESPIRATORY FAILURE *

By WM J KERR, M D, F A C P, and JOHN B LAGEN, M D,
San Francisco, California

It is our purpose to discuss one of the most important syndromes seen in the practice of adult medicine, and to suggest measures for symptomatic relief based upon knowledge of bodily mechanics and function. We refer especially to a type of obesity which appears to be exogenous in origin, arising in persons whose dietary habits lead to a caloric intake beyond their daily requirements. It is not easy to determine whether individuals with the relaxed habitus are predisposed to the train of events which follows, but it is apparent that when medical attention is sought these patients present the posture of relaxation. The gradual accumulation of adipose tissue in the normal depots for fat gives the appearance of rotundity, and the state is usually designated as corpulency. The accumulation of fat in the third decade is relatively symptomless. Friends will comment on the gain in weight, and subjects will note the expanding girth with the attendant strain on buttons and realize that they must discard belts for suspenders. At this stage some dyspnea will be noted on exertion, and a few suffer from symptoms referable to strain of the spinal column.

In the fourth decade the appearance of the individual is one of increasing corpulency, with a tendency toward a florid complexion. The normal curves of the spine are accentuated. The added weight of fat of the abdominal wall and viscera moves the line of gravity forward, and to compensate for this the major portion of the thorax is moved backward, accentuating the lumbar curve. The upper part of the thorax and shoulder-girdle move forward, increasing the normal thoracic curve, and the head and neck are thrust forward as is required for adjustment at a new line of gravity.

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From the Department of Medicine, University of California Medical School, San Francisco

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The resulting strain on the spinal column and its mechanical devices for maintaining the erect posture is great. At this stage symptoms arise which bring the patient to the internist, the orthopedist, the neurologist, the gynecologist, and specialists in almost every branch of medicine. If treatment is directed to symptomatic relief alone, the results are rarely satisfactory and recurrences are frequent. The use of mechanical appliances and postural training does not remove the real cause of trouble which arises through the accumulation of fat with its added weight forward of the normal line of gravity. Under such circumstances, postural training can minimize the strain in some measure, but only by increasing effort as the protuberant abdomen gains in the race with the individual's ability to compensate.

The fifth decade marks the period of transition from the state of physical well-being and activity of youth to one of gradual lessening of activity of middle and old age. There frequently occurs at this time a change in the habits of living, distinguished chiefly by diminution of active exercise or even normal activity, and by increase in the consumption of food. Finally, it is at this time of life that changes occur in the body which herald the onset of presenile degenerations. These are the depositions of fat, increased flabbiness of muscles, atheromatous changes in the blood vessels and those gradual changes in skin, connective and glandular tissue which are difficult to define. These latter may be described as loss of elasticity and reparability with consequent lessened tone and poor response to injury such as strain in muscles and ligaments or pressure on bone and cartilage.

The foregoing is the fate of most individuals who live to a sufficient age, though the time of onset, the rapidity of progression and the degree of bodily change vary greatly. These normal changes are prodromal to the onset of the postural syndrome, in fact may be considered to pave the way for its development. The syndrome itself is certainly modified or delayed in susceptible individuals by proper exercise and diet. Heredity may be a factor in its development, as shown by the familial occurrence of arteriosclerosis, arthritis, premature gray hair and particularly corpulency. Environment is directly related. The condition singles out those individuals of sedentary occupation who have little facility or desire for exercise. It is also prone to attack those whose station in life is such that ease is second nature, over-indulgence in rich food is possible, and for whom press of business may limit exercise. The most obvious result is the gradual development of a heavy, pendulous abdomen, the paunch or "watermelon belly" which was at one time almost pathognomonic of the individual having reached a certain age or position in life.

MECHANICS OF POSTURE

The upright position of the human species is phylogenetically one that has been developed from the original four-footed position. The chief, if not sole, support in this new position is the spine. Its main function is that

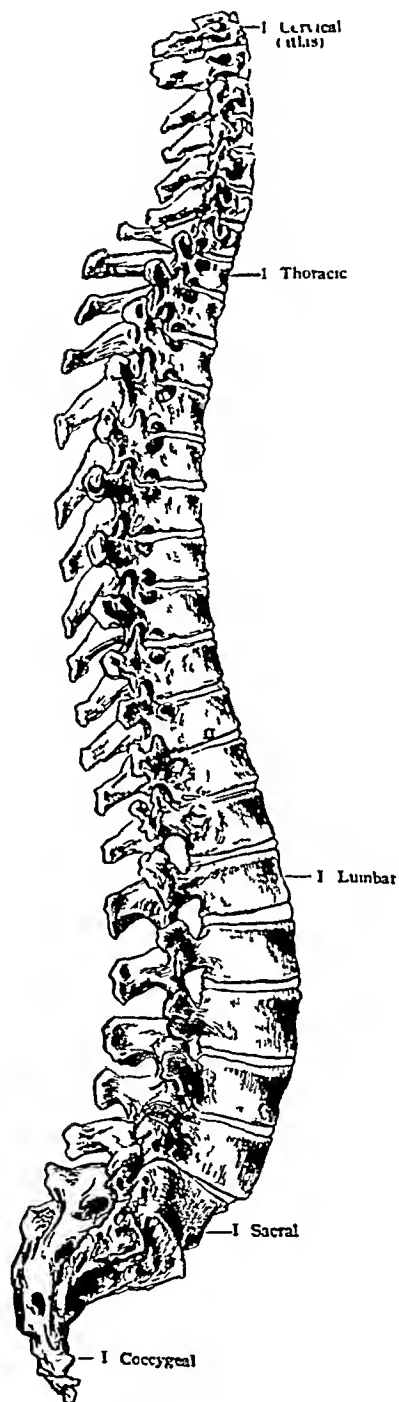


FIG 1 Lateral view of spine (after Piersol Human Anatomy, Reproduced by permission of The Macmillan Co)

of a sustaining rod which maintains the upright position of the body and carries its weight. From the first cervical down to the last lumbar, the vertebral bodies constantly increase in mass corresponding to the increase of the weight-bearing stress from above downward, as it is finally transmitted to the sacrum which latter's five segments rapidly decrease in mass from above downward (figure 1). The spine is also a balancing rod which is wedged into the pelvic ring and serves as a post of anchorage for the muscles of the back, themselves partly concerned in maintaining balance. Equilibrium maintained by the body in an upright or standing position is active and not passive, and muscular forces must constantly be engaged in opposing and neutralizing gravitational forces. Phylogenetically, attainment of the upright position by man required special development of the extensor muscles of trunk, hips, knees and ankles.

Steindler asserts, "A law of statics states that any force, if applied to a body, can be resolved into a translatory force and a so-called couple of rotating forces, the latter being so arranged that a line connecting their points of application goes through the so-called center of gravity. This center of gravity represents the one mass-point of the body which is so situated that the gravital force for all other mass-points of the body can be imagined to go through it." In man, it is located at about the level of the second sacral segment of the spine midway between the spine and a vertical prolongation of the hip-joints, in the midline. To quote again, "As long as all the partial forces of gravity apply in the center of gravity and as long as this center of gravity falls directly over the supporting surface, then the body is balanced and the resistant counterforces apply forces co-linear and in opposite direction to the gravitational force." This may be graphically represented by the line of gravity. Viewed from a frontal plane, this line of gravity bisects the body into two symmetrical halves. Viewed laterally, the line of gravity arises from the supporting surface of the feet between ball and heel, passes through the ankle- and knee-joints, runs between the hip-joint and sacrum and through the upper ventral portion of the sacro-iliac junction, then runs upward behind the bodies of the lumbar spine, intersects the spine at the lumbothoracic junction, runs slightly in front of the thoracic spine, intersects the spine again at the cervicothoracic junction, runs slightly behind the cervical vertebrae, and touches the head behind the ear at the mastoid process (figures 2 and 3).

There is an inherent tendency in the individual to maintain the center of line of gravity at a constant relation to the points of support of the body. Usually the line of gravity falls about four centimeters in front of the center of the ankle-joint. If morphological changes occur in the body which attempt to move the center of gravity forward, for instance in pregnancy or in obesity, we see that this tendency is usually counteracted by an increased plantar flexion of the foot in the ankle-joint. Naturally this applies only to a certain degree, and excess weight will finally carry the center of gravity

forward, thus forcing the knees into flexion in order to bring the line of gravity forward also

MECHANICS OF RESPIRATION

The thorax is a semi-rigid cavity entirely shut off from the outside by the structures of the neck above, by the ribs and spine on the sides, and by the diaphragm from the abdominal cavity below. The thorax contains the

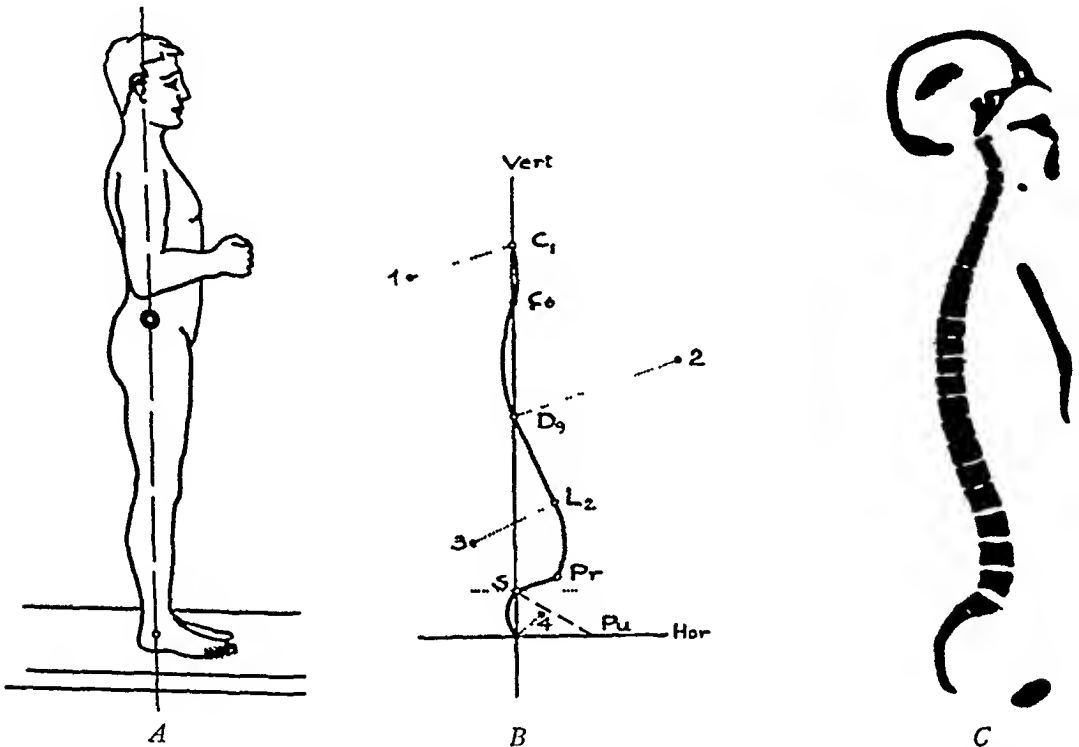


FIG 2 Vertebral column showing curves as seen actually and in silhouette (From Steindler's "Mechanics of Normal and Pathological Locomotion in Man", Courtesy of Charles C Thomas, Publisher)

- A Normal upright posture showing line of gravity and center of gravity
- B Intersections of the line of gravity
- C Dorsoposterior curves

heart, great vessels, esophagus, trachea and lungs, which latter alone interest us. The lungs may be considered as two large membranous sacs whose interior surface is multiplied greatly by subdivision into alveoli, all of which communicate freely, by gradually enlarging tubes (the bronchioles and bronchi), with the outside air. The atmospheric pressure on the alveoli expands the lungs until they fill the entire thoracic cavity not occupied by other organs, so that however the size of the thoracic cavity varies, the volume of the lungs must change accordingly. Normal respiratory movements consist of an active inspiration followed by a passive expiration, the former requiring muscular activity, the latter usually not, except during forced respirations. The amount of air that flows in and out with each normal

respiration is known as the tidal air, and averages about 500 c c for an adult male. The complementary air is the amount of air that can be breathed in over and above the tidal air by the deepest possible inspiration, it is about 1600 c c. Conversely, the supplemental air is the amount that can be breathed out, after a quiet expiration, by the most forcible expiration, it is also about 1600 c c. The vital capacity equals the tidal plus the supplemental plus the complementary air.

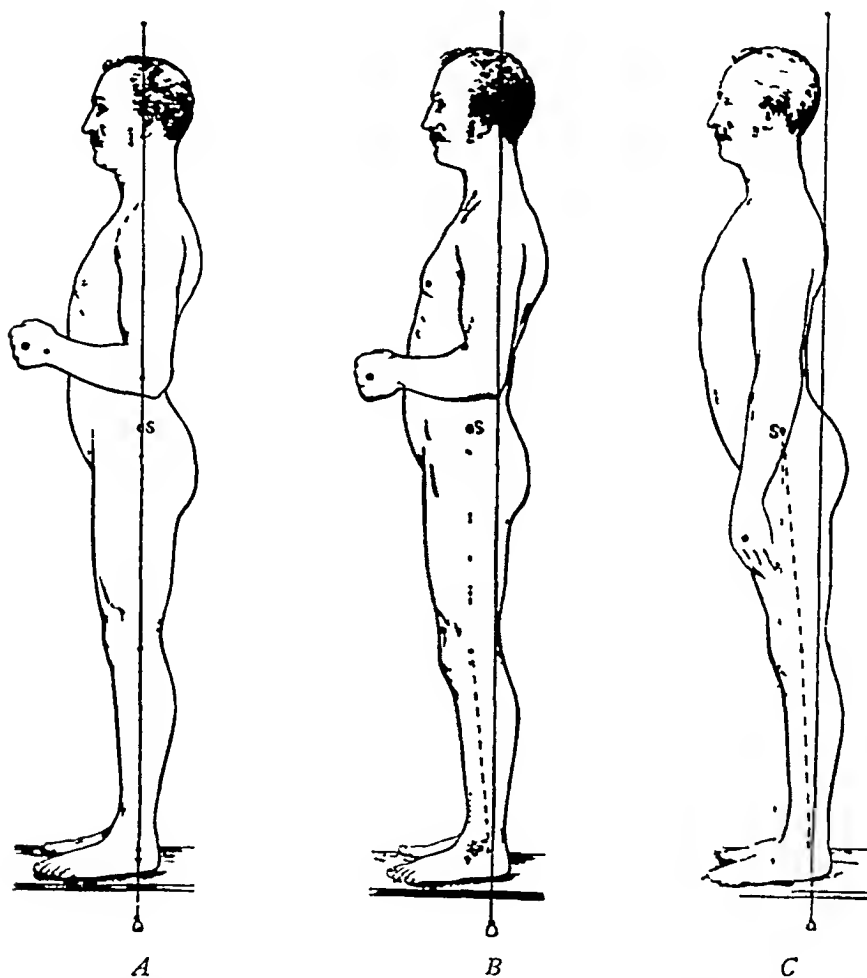


FIG 3 Types of posture (From Steindler's "Mechanics of Normal and Pathological Locomotion in Man", Courtesy of Charles C Thomas, Publisher)

- A Normal posture
- B Relaxed posture
- C Military posture

Each rib is attached to the spinal column at two points: the head to the body of the vertebra and the tubercle to the transverse process, so that up and down movements of the ribs result in a rotation around an axis joining these two points. Since the ribs slant downward to their attachment to the sternum, this with the rotation causes an enlargement in the dorsoventral

and lateral diameters of the chest every time the ribs move up, which is the act of inspiration. Therefore any muscle attached to the thorax whose contraction causes an elevation of the ribs must be considered an inspiratory muscle, and conversely, anything which elevates the ribs results in an inspiratory state of the thorax.

To the six lower ribs and to the xiphoid process are attached the costal and sternal portions of the diaphragm respectively, the lumbar portion attaches to the first, second, third and fourth lumbar vertebrae, and the thoracic portion to the thoracic vertebrae. From these attachments the muscular sheet extends ventrally along the walls of the thorax and then bends over to form an arch, with all the fibers inserting in the central tendon. This latter is not entirely free since the pericardium is attached to it, and may be considered as a tendinous attachment connected with the cervical fascia. A contraction of the diaphragmatic muscle draws the central tendon downward toward the abdominal cavity and therefore increases the size of the chest in the vertical diameter, while an increase in the thoracic cavity around the periphery of the diaphragm is caused also by the flattening of the muscular arch. Two results follow this movement: the lungs are expanded exactly in proportion as the cavity enlarges, which constitutes an inspiration; secondly, the descent of the diaphragm raises the pressure in the abdominal cavity, causing the abdominal wall to protrude. Expiration, as far as the diaphragm is concerned, is entirely passive, resulting from relaxation of the contraction, though aided by the abdominal pressure produced by inspiration, and still further, on forced respiration, by contraction of the abdominal musculature. Conversely again, anything which causes the diaphragm to descend results in an inspiratory stage of the thorax.

THE POSTURAL SYNDROME

Description The postural syndrome has as its basis obesity, which results in the development of a heavy dependent abdomen. It is this latter which is the obvious cause of the train of symptoms and signs that ensues. Their production depends upon two factors, unrelated except for cause, but synergic in effect. The first of these is the dragging effect exerted by the increased abdominal weight. This makes itself felt chiefly in the lumbar spine to which the weight is transmitted through muscle, fascia and skin. Here the result is at first an exaggeration of the normal lumbar curve, later an increasing lordosis with the vertebrae parting ventrally like the leaves in a book. The spine being intimately associated throughout its length, must compensate for this, which it does by causing a thoracic kyphosis and a cervical lordosis. The sacrum, normally at an angle of 45 to 60 degrees with the lumbar spine, is elevated to an angle of 90 degrees or more.

The second factor is concerned with the shift in the center of gravity produced by the excess weight which, as it were, has been attached to the front of the body. As mentioned previously, this is at first compensated for

by increased plantar flexion. When this is no longer effective, the individual is forced to compensate further, which he does by bending his knees and voluntarily increasing the lumbar lordosis through muscular action, the latter resulting also in the effect on the rest of the spine. A patient seen in lateral aspect reminds one of an individual who is attempting to "get in under" a heavy weight in order to support it more comfortably. This is somewhat



FIG 4 External resistance weight lifting (From Steindler's "Mechanics of Normal and Pathological Locomotion in Man", Courtesy of Charles C Thomas, Publisher)

A From the floor

B To shoulder height

C Upward lift

(Note the weight following closely in the line of gravity)

similar to that which is seen in the mid-stage of lifting an external weight, as shown in figure 4. Here of course some of the weight is supported by the muscles of the arm and shoulder, and exerts a drag on the upper part of the frame also. Note the bending of the knees and the increase in normal spinal curvature.

The governing principle is that the weight to be lifted never becomes too far deflected from the line of gravity, otherwise a rotation movement will

develop which is too great to be overcome by the working muscles. With the weight in the line of gravity, the individual has only the translatory weight-stresses to overcome, and he will avail himself of the skeletal resistances for this—that is, the resistance of the rigid bones—to the best possible advantage. An analogous situation is seen in patients with abdominal obesity. Here the center of gravity has been shifted forward from the line of gravity. In order to maintain this weight with the least muscular exertion and therefore the greatest comfort, the line of gravity (which is the optimum line of weight-bearing) must be carried forward. This is done, as already stated, by bending the knees and increasing the lumbar lordosis (figure 5).

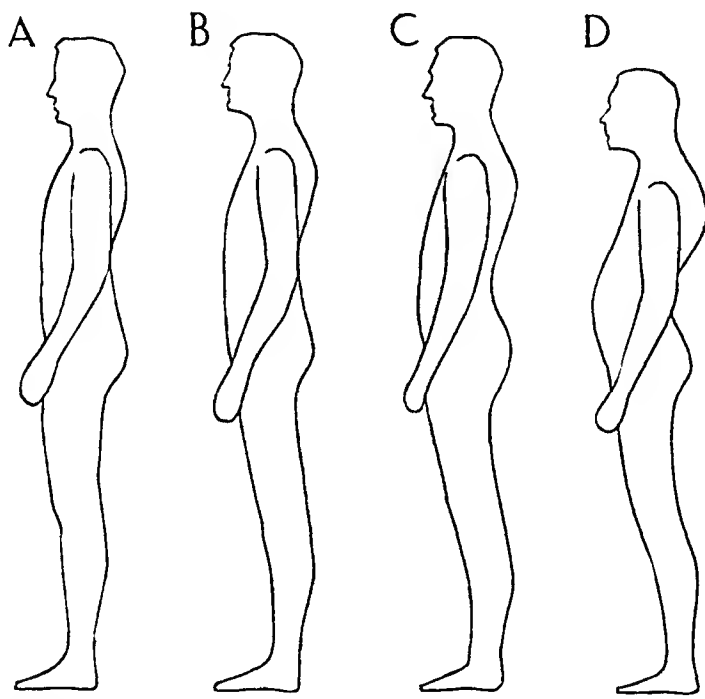


FIG 5 Figures illustrating good and bad bodily mechanics, based on an examination of 700 Harvard freshmen (after Lee and Brown in "The Journal of Bone and Joint Surgery", reproduced by permission)

Group A 75%
Good mechanical use
of the human body

- 1 Head straight
above chest,
hips and feet
- 2 Chest up and for-
ward
- 3 Abdomen in or
flat
- 4 Back, usual curves
not exaggerated

Group B 12.5%
Fairly good mechan-
ical use of the hu-
man body. Note
changes from
Group A

- 1 Head too far for-
ward
- 2 Chest not so well
up or forward
- 3 Abdomen, very
little change
- 4 Back, very little
change

Group C 55%
Bad mechanical use
of the body. Note
changes from
Group A

- 1 Head forward of
chest
- 2 Chest flat
- 3 Abdomen relaxed
and forward
- 4 Back curves are
exaggerated

Group D 25%
Very bad mechanical
use of the body
Note changes from
Group A

- 1 Head still farther
forward
- 2 Chest still flatter
and farther back
- 3 Abdomen com-
pletely relaxed,
"slouchy"
- 4 Back, all curves
exaggerated to
the extreme

Whichever the mode of production, the effect of the increase in lumbar lordosis is the same, resulting as it must in the compensatory increase in the other normal spinal curves. This accentuation of the curves, coupled with the bending of the knees, causes a reduction of stature. The increase in cervical lordosis forces the individual to carry his head bent forward, the degree depending upon the lordosis. To maintain the head in the normal position puts extra work on the extensor muscles of the back of the neck, so a position of comfort unconsciously results in the bowing of the head. Thus, however, necessitates a strain on the extra-ocular muscles (recti-superior), it being easier to lift the eyes than to lift the head. Hypertrophic arthritis of the spine may be initiated, or exacerbated if already present. In particular, the radicular syndrome due to arthritis is usually made worse, or may make its first appearance when the increasing spinal curvature in the presence of the arthritis results in irritation of nerves.

The increased thoracic kyphosis is perhaps the most important effect of all in view of the result it has on respiration. This is of far-reaching importance and not limited alone to inspiration and expiration. Any increase in the normal curves of the thoracic spine, as shown by Kountz and Alexander, results in elevation of the ribs, producing thereby the barrel-chest seen typically in obstructive emphysema, but in this instance without marked emphysematous changes in the lungs. This flaring of the rib-cage also directs the lower ribs downward, which with the widening, flattens the diaphragm. Part of the mechanism that lowers the diaphragm and prevents their excursion is due to the visceroptosis.

Another significant fact is that these individuals are able to breathe with a great deal more facility when lying flat, since the relief from abdominal weight in the prone position must release the diaphragms. They suffer, not from orthopnea, but from *orthostatic dyspnea*.

There is therefore a double mechanism at work to keep the chest more or less fixed in the inspiratory phase. Consequently the tidal air is less than normal, while the complemental air is greatly reduced. Expiration may be even more affected than inspiration. There is little tendency for the chest to collapse or the diaphragm to raise at the end of inspiration, passive expiration is reduced. Expiration must now become somewhat of an active muscular exertion, and mainly thoracic since the marked visceroptosis prevents muscular exertion on the part of the abdomen to force up the diaphragm. There is not, however, the added impediment of bronchiolar narrowing as is seen in obstructive emphysema.

The reduction in pulmonary ventilation, leading to oxygen-debt on exertion particularly, results in dyspnea. This, as stated before, is orthostatic, occurring only in the upright position, but is not present on sitting or in the prone position. There is a compensation taking place, however, which is the occurrence of polycythemia in the advanced stages of the syndrome, brought on by the reduced oxygenation of the blood. This often produces

some cyanosis, or accentuates that already present. The late effects are on diminution of cardiac reserve from overstrain, constituting, in its effects on tissue-oxygenation, somewhat of a vicious cycle. Coincident arteriosclerosis complicates the clinical picture. Figure 6 shows in tabular form the inter-relationship of the syndrome.

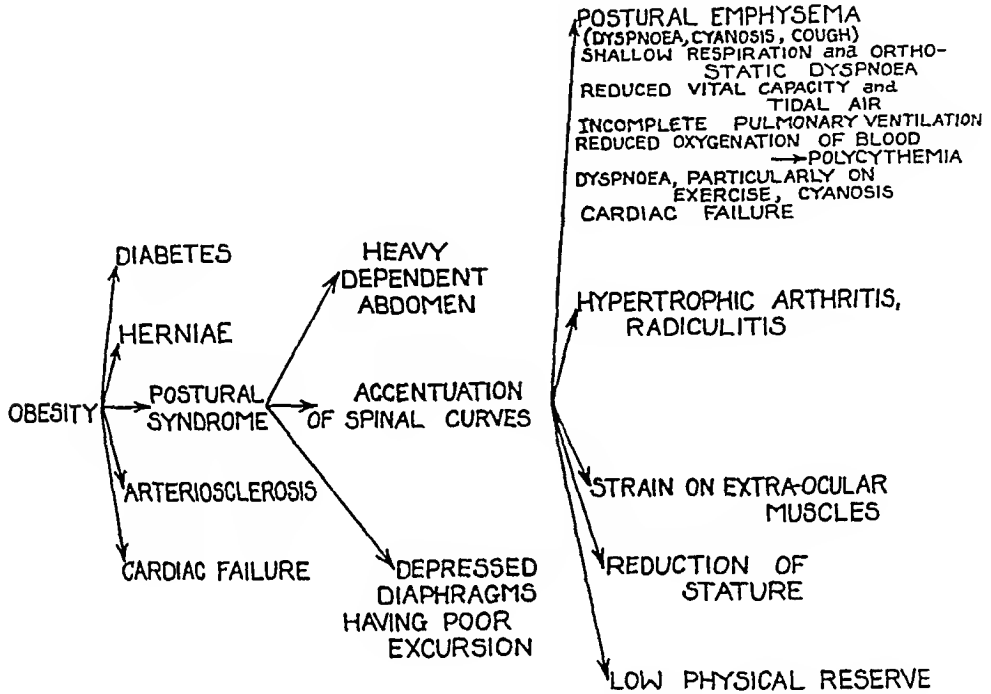


FIG 6 Schematic representation of the postural syndrome resulting from obesity

Symptomatology It is during the fifth and sixth decades that patients in this group are obliged to seek medical advice from the internist. The clinical syndrome is, as a rule, remarkably complete. The presenting symptoms are usually increasing *orthostatic dyspnea*, cough, cyanosis and edema, referable to the respiratory and circulatory systems. Along with these, or as chief symptoms, are radiculitis associated with "irritation" of nerve-roots, a group of less well-defined symptoms originating in the vertebral bodies, intervertebral discs and ligaments, symptoms resulting from muscular strain and weakness, including pains in the orbits associated with strain on the extra-ocular muscles and such obvious defects as ventral and inguinal herniae, symptoms of strain on the lumbosacral and iliosacral articulations, and symptoms of strain on the hip- and knee-joints and the arches of the feet.

The physical examination may be made for the first time with the patient in bed suffering from respiratory and circulatory symptoms. In such emergencies, the full clinical picture may not be readily appreciated. The extremely florid complexion, with cyanosis, cough and edema, direct one's attention to the cardiorespiratory apparatus. The emphysematous chest

interferes with proper examination of the heart The blood pressure is normal or slightly elevated The abdomen is full, and a large accumulation of fat locally is often mistaken for ascites The great protuberance of the abdomen can be appreciated only when the patient is able to stand The kyphos in the upper thoracic spine may be so marked that such patients while lying almost horizontal in bed, will hold the neck and head in a vertical position The examination of the blood shows usually a hemoglobin content above 100 per cent (Sahli), and the red blood cells above 5,000,000 per c c Percentages of hemoglobin of 110 per cent, and red cells above 6,000,000 are not uncommon The vital capacity at this, the late stage, is usually reduced With proper treatment for congestive cardiac failure, the balance is soon reestablished in most cases It is surprising to observe the promptness with which patients are able to rest in the recumbent position, in contrast to patients with congestive cardiac failure from other causes When these patients become ambulatory, they exhibit extreme examples of the postural defects which will now be described

The appearance of the patient when fully undressed, and when viewed at a distance from the side is one of extreme relaxation The most striking feature is the rounded protuberant abdomen, but upon further inspection it is apparent that the entire outline of the silhouette is altered The curves of the spine are all accentuated, there is a moderate or marked lordosis of the lumbar spine, the sacrum is more horizontal than normal, and the thoracic spinal curve is increased with the shoulders forward and the arms suspended in front of their normal position, the upper ventral thoracic region is depressed, the head and neck are well forward with the chin out, accentuating the increasing kyphos in the upper thoracic spine, the eyes are elevated to retain vision in a horizontal direction, the pelvis is rotated backward, and the legs are flexed at the knees The stature is shortened more or less, and sometimes patients state that they have lost two or more inches in height from their measurements earlier in life They have the appearance of stooping to avoid an overhead obstruction Several have remarked that their friends ask why they always stand as if they were entering a low tunnel (figure 7) They have the appearance in outline of women in the later months of pregnancy, which may be duplicated in the normal individual by holding in the hands or by suspending in front of the abdomen a heavy weight (figure 8) If such faults in the distribution of weight were not corrected by re-alignment through the shifting of other masses of the body, the individual would be unable to maintain the erect posture (figure 9)

A more detailed study of the skeletal alterations in this syndrome is of interest The lateral roentgenograms, when taken in the position naturally assumed by the patient, show well the accentuation of the spinal curves and some of the alterations of individual vertebrae and intervertebral discs In the two regions where lordosis is produced—namely, the lumbar and cervical segments—the vertebral bodies tend to separate at their ventral margins with

their articulating surfaces in line with radii converging at a point nearer to the spine than is normal. This is particularly striking in the lumbar vertebrae, which seem to spring apart ventrally like short leaves of a book. The intervertebral discs are wedge-shaped in appearance, filling the spaces. The

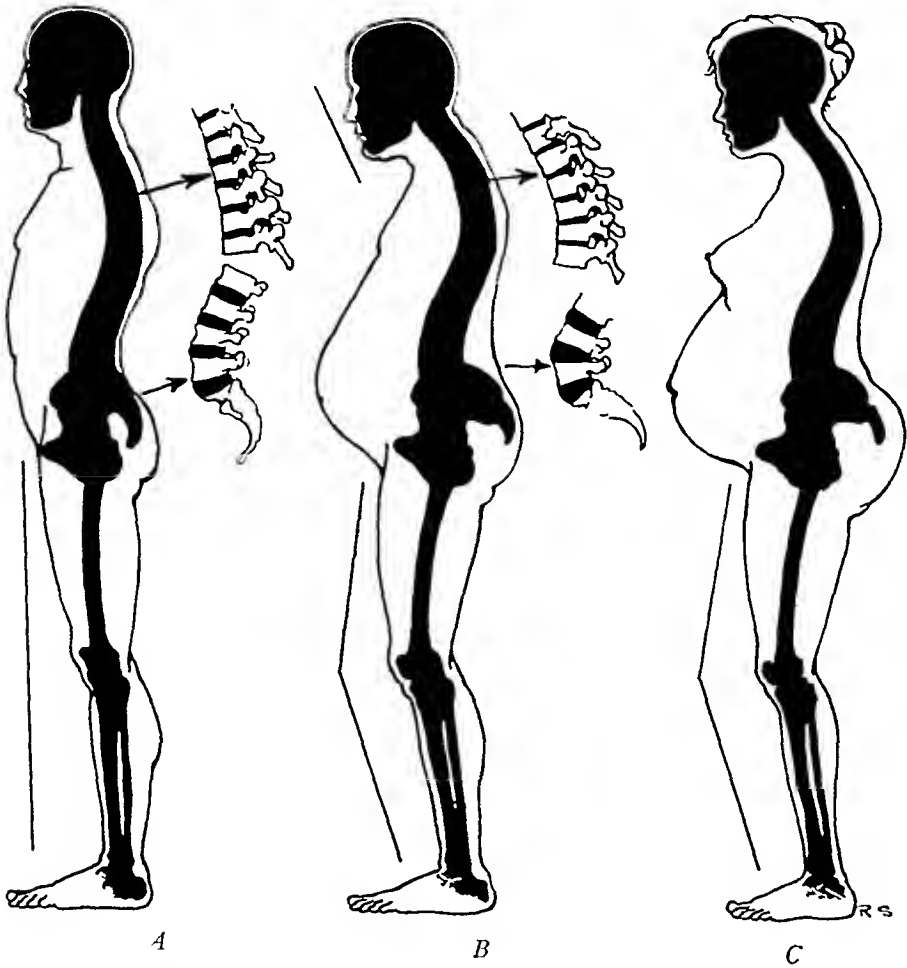


FIG 7 Types of posture showing effects on spine

- A* Posture, spinal curves and intervertebral discs normal
B Relaxed posture with accentuated spinal curves resulting from a pendulous abdomen
C Postural changes late in pregnancy similar to those in *B*, but which never persist long enough to affect the intervertebral discs

lumbosacral articulation is likewise wider open ventrally than normal, and the weight-bearing surface seems to be limited to a narrow zone at the dorsal margin of the junction. The sacrum lies more horizontal than is normal, and the upper inlet of the pelvis is tilted backward and downward with the accompanying elevation of the acetabulum. The femur is inclined forward from the vertical line at its lower end and the knee flexed slightly. In the thoracic spine the dorsal convexity is increased unless an associated ankylosing arthritis prevents this compensating movement. At some sector of the

thoracic spine the vertebral bodies tend to be compressed ventrally, and wedge-shaped, and the intervertebral discs share likewise in a similar deformity. The kyphos of the upper thoracic spine is sometimes very marked, with an appearance of the vertebral bodies resembling a crushing "jack-

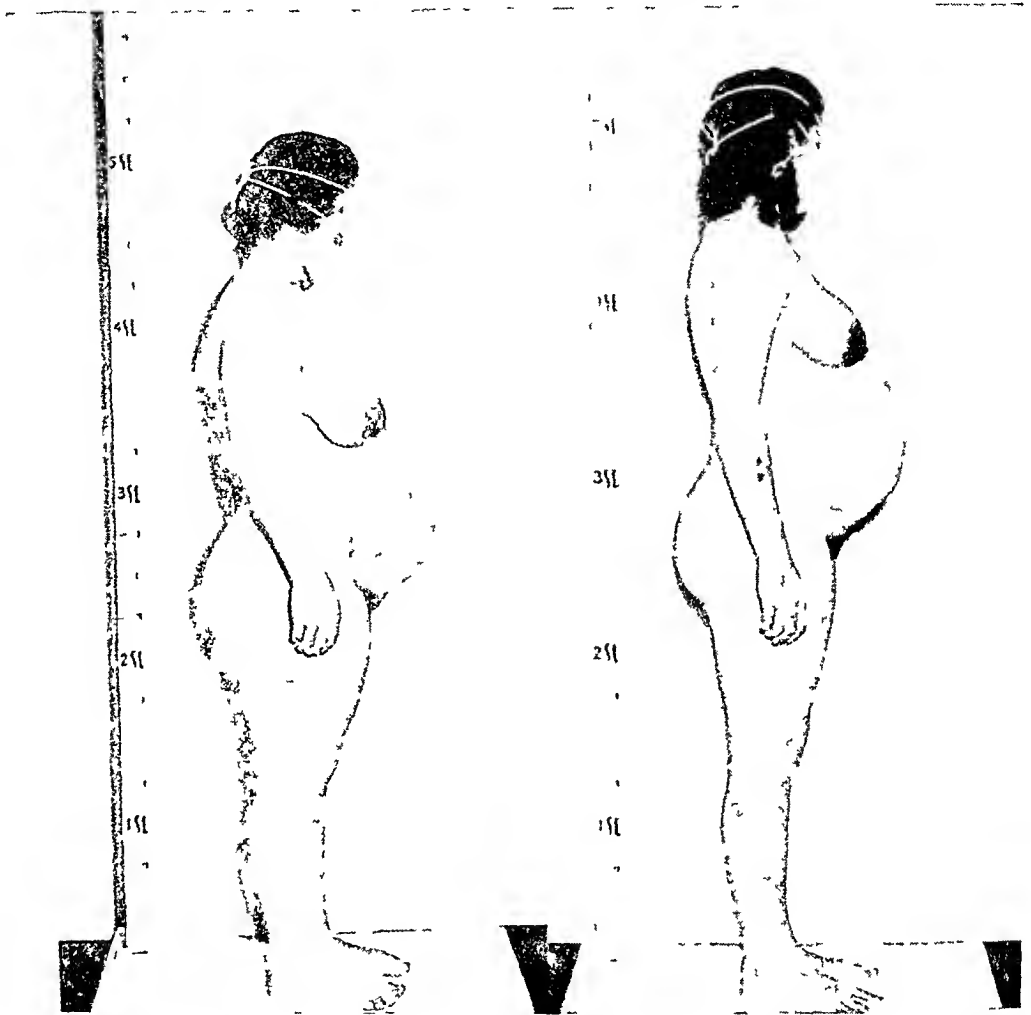


FIG 8 Lateral views of women in the late weeks of pregnancy, showing accentuated spinal curves

knife fracture'. The margins of the vertebrae and their articulations with the ribs frequently show lipping and spurs designated as hypertrophic arthritis. In the degenerative changes accompanying old age, the mechanical factors in faulty posture probably determine the location of these changes and may be more important in their causation than is generally understood.

Examination of the thorax shows some of the obvious effects of the faulty posture. In the usual posture on relaxation, the ribs stand in a more horizontal position than normal and incapable of normal elevation and expansion of the lungs. With respiratory effort, such as is made when per-

forming the test for vital capacity, the full expansion can be attained in the uncomplicated case. The diaphragms move the normal distance, or nearly so, on effort, but in ordinary breathing in the upright position it is obvious on auscultation that the expiratory phase is prolonged. The upper and

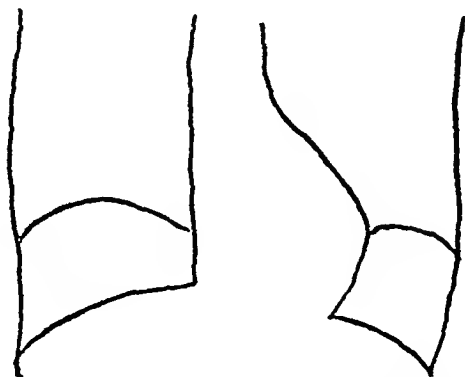


FIG. 9. Silhouettes of a woman late in pregnancy and a man with a pendulous abdomen.

ventral portions of the lungs are hyperresonant, as well as the bases behind. The veins in the neck and of the shoulder-girdle may be distended. Fluoroscopic examination of the chest usually shows little or no cardiac enlargement in the early stages, and in many cases the heart appears small. The emphysematous areas show increased illumination. The diaphragms move downward readily on forced inspiration and it is of some interest to note

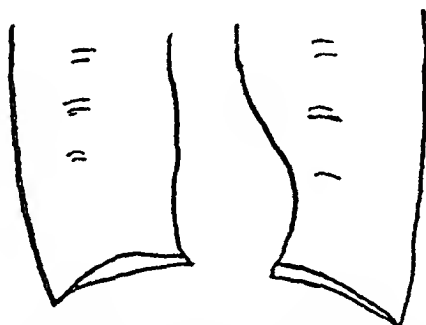
that toward the end of inspiration there appears to be a sudden acceleration of the movement, to be followed by a long and slow ascent of the diaphragm before the next inspiration (figure 10) The interference with the dia-

1



ORTHODIAGRAM OF MAXIMUM DIAPHRAGMATIC EXCURSION IN A PATIENT WITH POSTURAL EMPHYSEMA

B



ORTHODIAGRAM OF MAXIMUM DIAPHRAGMATIC EXCURSION IN A PATIENT WITH ASTHMA AND OBSTRUCTIVE EMPHYSEMA

Fig 10 Orthodiagrams of diaphragmatic excursion (after Kountz and Alexander in "Medicine", reproduced by permission)

phragmatic movements by the defects in posture, and the added weight of the visceral fat, combine to prevent normal aeration of the lungs. Hansson discusses the mechanical importance of good posture as follows: "The diaphragm arises from the costal cartilages, xiphoid process, transverse process of the twelve 'dorsal' vertebrae, and from ligaments of the psoas muscle. The diaphragm can only be anchored rigidly if the back is held in extension, and thus poor posture diminishes the diaphragmatic excursion. The stomach is attached to the diaphragm at the cardiac end, and the pyloric end is fixed to the body wall. The liver is partly suspended from the diaphragm, and the transverse colon indirectly, by means of the mesocolon. A great load is, therefore, carried by the center of the diaphragm which, at least partially, is held through the right pericardium by the continuation of the

cervical fascia This fascia is attached to the cervical spine and mastoid process It can be understood, therefore, how flexion of the head and neck relaxes the cervical fascia, causing a ptosis of the viscera in the lower abdomen and pelvis Thus, it is of importance to carry the chin in and the head back "

The vital capacity of the lungs early in the evolution of the syndrome is normal, but as the thorax changes shape after many years of faulty posture there is gradual reduction in vital capacity This is, in part, due to the great mass of fat in the upper abdomen, and in part to the loss of elasticity in emphysematous areas of the lung At first the contrast to obstructive emphysema is great, but in the terminal stage of postural emphysema the vital capacity may be markedly reduced also Of greater importance is the tidal air of ordinary respiration Although we have not been able to verify our impression that the tidal air is greatly reduced, because of the difficulties in getting patients to breathe without conscious effort under experimental conditions, there can be little doubt of such reduction under given circumstances One of the striking symptoms described by such patients is dyspnea in the upright position, which we have designated as *orthostatic dyspnea* Almost invariably, except in the terminal stages when secondary cardiorespiratory complications have arisen, such patients will be able to lie in the prone position without respiratory embarrassment The reasons for this are obvious when the foregoing comments are recalled the thorax is extended, the diaphragmatic attachments are now in a more fixed position and the *abdominal counterweight* which must be lifted at great expenditure of energy in the upright position now becomes a minor encumbrance during expiration The counterweight, through gravity, may now actually assist in the ascent of the diaphragm in expiration, and the elasticity of the lungs becomes a more effective agency in the exchange of gases These considerations must be kept in mind in treatment, and will be reviewed later on in consideration of the management of the patient

The respiratory and circulatory disturbances are complex and difficult to analyze The faulty exchange of gases apparently leads to a compensatory polycythemia, which in our series is relatively constant The facies of the patient is one of high reddish color with variable cyanosis of the lips and cheeks depending on the stage of the complications in the thorax The veins over the upper thorax and arms, and in the neck, are usually prominent, and sometimes the subclavian veins are mechanically compressed between the clavicles and the first rib These latter veins may empty well when the shoulders are elevated The heart may be small, normal or of large size, apparently depending on many factors Here we must consider the degree and stage of emphysema and the immobility of the diaphragm interfering with the filling of the right heart, the extent of pulmonary arteriosclerosis and state of the right heart, the extent of systemic and coronary arteriosclerosis with and without hypertension, and the deformity

of the thoracic spine The position and shape of the heart are influenced by the position and movements of the diaphragm Electrocardiograms show more often a tendency to right axis deviation, but sometimes left axis deviation especially in patients with hypertension Defects in the conduction system and arrhythmias may be observed in older subjects Cardiorespiratory complications usually lead to an untimely death

The radicular symptoms and signs are of frequent occurrence, extending over many years They are related to the deformities of the spine, and have been previously reported in a general discussion of the subject by Gunther and Kerr, and many others Of special interest in our patients with the postural syndrome has been the history of attacks of "lumbago," lumbosacral and sacro-iliac strain, sciatica, abdominal and thoracic crises, and "neuritis" of the cervical and occipital nerves In some cases abdominal and pelvic operations are performed unnecessarily About one-third of all patients referred to us for supposed cardiac pain have their symptoms on the basis of spinal disease in the thoracic region, and are relieved by correction of the postural defects "Pseudo-angina" can be interpreted only as false diagnosis Many patients are treated for pain of suspected cardiac origin, and are subjected to the anxiety which such an interpretation connotes, who could be restored to a comfortable and useful life Gunther and Sampson have reported on this subject from our clinic

The accumulation of fat in the abdominal wall is great in such subjects The lack of proper exercise and function of the abdominal muscles results in atrophy and the weight of the mass of fat within and without the peritoneal cavity causes stretching of these damaged tissues Herniae in the midline and at the sides of the recti abdominis muscles, especially at their upper ends, are of common occurrence Inguinal herniae are also frequently associated with strain on the abdominal muscles resulting from the extreme weight placed upon them at the nearly horizontal shelf which limits the protuberant abdomen just above the pubis

The association of arteriosclerosis and diabetes with the postural syndrome may be related to obesity or other causes However, these conditions frequently complicate the clinical problem and must be dealt with in treatment Pulmonary arteriosclerosis is sometimes an added burden to an already overworked cardiorespiratory apparatus

Diagnosis and Differential Diagnosis The diagnosis of the postural syndrome described is usually not difficult In the relatively symptomless period subjects show a tendency to increasing weight with emphasis on expanding girth The compensatory changes in the spinal curves are remarked Episodes of thoracic and abdominal crises and "attacks" of spinal origin designated as neuritis, sciatica, "lumbago," lumbosacral or sacro-iliac strain often cause the patient to consult the orthopedist, neurologist and gynecologist and less frequently the internist The "spinal adjuster" sees many of these patients, also, and frequently after relief is not forthcoming from general practitioners and specialists

The respiratory symptoms and signs are minimal in these early stages. There may be slight dyspnea on exertion but it is usually attributed by the patient to his gain in weight. Orthostatic dyspnea has not become marked.

With advancing years the effects upon the respiratory apparatus assume greater prominence and the evidences of strain upon structures supporting the deformed body in the upright position manifest themselves. The increasing distortion of the abdomen and the exaggeration of the spinal curves are obvious. The orthostatic dyspnea becomes pronounced. The patient shows a high color and frequently presents a slight polycythemia. The vital capacity is reduced slightly but the tidal air is apparently greatly reduced only in the upright posture. The symptoms and signs of radiculitis are often marked. The roentgenographic evidence of abnormalities in the spinal axis usually confirms and helps to explain the radicular manifestations.

In differential diagnosis we must consider obstructive emphysema and other pulmonary diseases, cardiovascular disease, especially generalized, and pulmonary arteriosclerosis which may be present in older subjects, and spinal disease leading to deformities and radicular symptoms. With advancing years it is not always easy to disentangle all the complicating factors which give rise to confusion in diagnosis.

Treatment Prophylactic treatment would, of course, be most rational. Unfortunately, those who have a tendency to exogenous obesity (those who could personally do something about it) disregard the laws of the conservation of energy through ignorance or neglect. Sedentary habits and over-indulgence in food are sure guides to obesity for a great majority of people approaching middle life. The automobile and other means for conserving energy are making the individual more toad-like. Attention to the diet and exercise will benefit the great majority of those who are approaching middle age. The cultivation of the postural reflexes will also be helpful for those with relaxed habitus.

It is unfortunate that those who manifest symptoms first in relation to spinal strain are treated improperly from a mechanical viewpoint. There may be justification for the use of casts, braces, strapping and other mechanical devices to carry the patient over the acute crisis, but, when this episode has subsided, other measures must be instituted to prevent their recurrence or the more serious results which develop through the coming years. The postural training and exercises, of which Goldthwait has been such an able exponent in this country, may be very helpful in overcoming the postural defects. They may postpone or minimize future complications. Support for the abdomen may likewise tend to restore the normal distribution of weight and line of gravity, but these measures are only makeshifts for the obese patient. There can be no real substitute for the removal of excess weight by whatever means are possible, but chiefly through restrictions in diet and increased exercise. When all these measures are combined

we can offer the best plan for restoration of normal function. Without reduction of weight and especially of the abdominal region, we are frustrated in our efforts to secure the best results.

In the treatment of our patients, mostly males in the fifth and sixth decades, most of whom have appeared in the later stages of the syndrome, we have been confronted with symptoms of marked severity. However, those with less marked symptoms have responded well to the same measures. The point of attack is in three directions, but with the same end in view:

- 1 Temporary elastic support of the pendulous abdomen
- 2 Reduction in weight
- 3 Postural exercises

1 *Elastic Abdominal Support*—It occurred to one of us that if the patient could be given an abdominal support to overcome some of the weight applied to the diaphragm during inspiration and to relieve the *counter-weight* during expiration, the tidal air would be greatly increased, the spinal curves would be straightened, and the line of gravity moved backward. If a belt were devised which gave abdominal support and if elastic materials were inserted in the belt at the sides of the abdomen, the tidal air could be further enhanced. These elastic materials would in effect serve as a method of giving the patient artificial respiration by assisting in the expulsion of gases from the lungs. The description of this belt is given, and view of the belt in position in figure 11.

Many belts have been devised and are used routinely for abdominal support. Their main purpose is to correct either obesity or ptosis of the abdomen by lifting and holding in the abdominal wall. They accomplish this by supplementing or replacing the abdominal musculature which has either lost its tone or, more usually, has become flabby and no longer functions properly. These belts are constructed in many ways, but all have similar materials and serve the same purpose. We have a collection of inadequate belts donated by patients, and these show great variation in type.

The belt that we are presenting embodies several new principles. As a whole it is not unusual, or very different from the many we have seen. However, it is constructed with the physiological function of the abdominal wall in mind, and is designed to supplement and aid the ventral muscles rather than to replace them. A tightly wound cloth binder would support the abdomen more efficiently but would not permit mobility necessary for respiration.

Figure 11 C shows the belt in place on a patient. Figure 11 B shows some of the details of construction. The supporter is made of coutil, pekin-stripe cloth and elastic goring, it is fastened on by stake-buckles and hooks.

The front sections and the back section are of double thickness. The outer layer is of high quality coutil, the inner of pekin-stripe cloth. The only difference between the two is in the softer and finer quality of the pekin-stripe material which, being next to the skin, prevents chafing. Both sections are tailored, or fashioned. There

* These belts have been made for us by the C. H. Hittenberger Co., 1103 Market St., San Francisco. We wish to express our appreciation to this firm for helpful criticism in the original designing of the belt and for their courtesy and care in fitting our patients.

are three double stays in the back section with a seam at each, which permits fashioning the supporter to fit the contours of the individual patient. The back section is $8\frac{1}{2}$ inches in height, and the stays are of whalebone. For conditions of extreme lordosis, the cloth section in back may be extended up to the twelfth thoracic vertebra, and have incorporated in its firm duraluminum or steel stays. The stays should not, however, be bent to fit the curve of the lumbar spine but should touch the body at only the upper and lower edges of the belt, allowing the middle to span or bridge the lordosed spine.

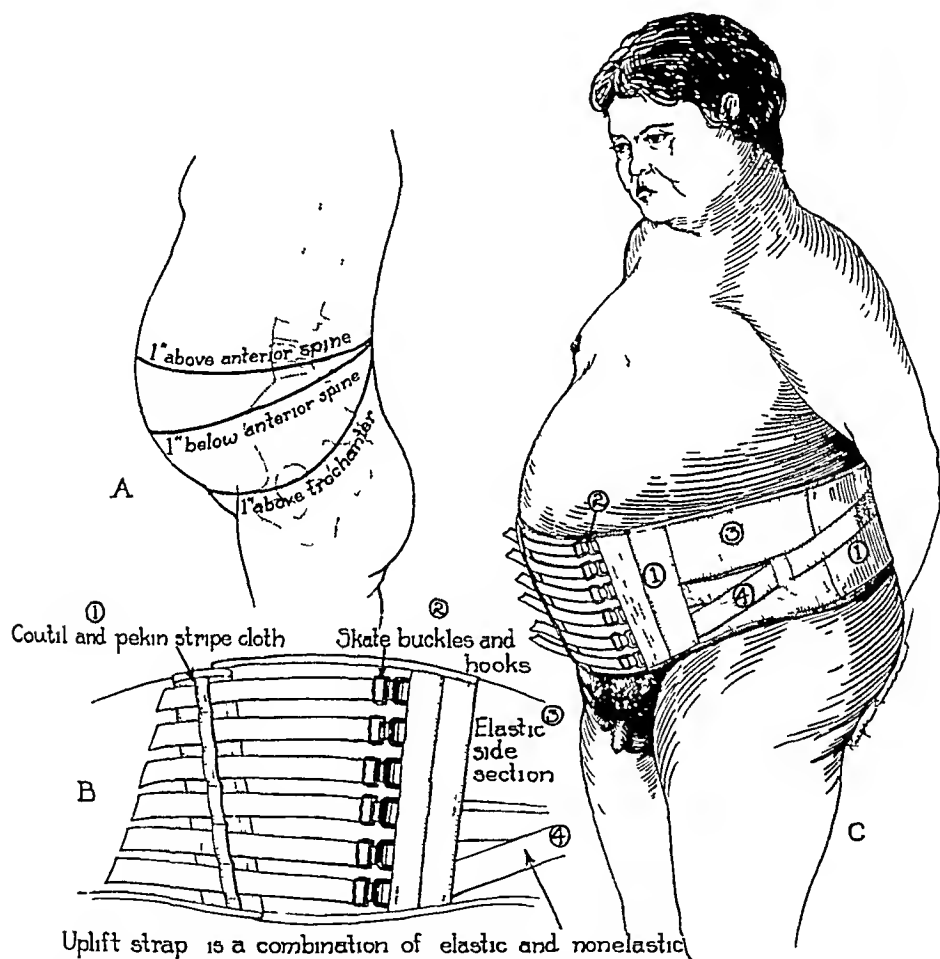


FIG. 11 Showing the details of the belt suggested for the treatment of obesity and postural emphysema, and the locations for measurements to be used in the construction of the belt.

The left front section (figure 11 C(1)) has the hooks attached to it. The right front section (figure 11 B(1)) has attached to it the straps carrying the buckles. The height of the front from top to bottom varies somewhat according to the circumference. For patients 38 inches in circumference at the crest of the ilium, a height of 9 inches is usually most satisfactory, if the patient is exceptionally tall a front height of 10 inches can be used to advantage, for patients of a circumference of 44 inches or more, a height of 10 to 12 inches is usually required. The left front section extends across the abdomen as a flap 6 inches long, padded between the two layers with strips of drusy-cloth. This provides a soft base for the straps to lie on. The width of each half of the cloth section across the front is considerably less than in the

usual supporter, being an average of $2\frac{1}{2}$ inches wide. The total width of the non-elastic front is about 5 to 7 inches, but this varies with the tightness of the belt. The front flap slips under the right side of the belt as it is tightened.

The elastic lateral sections (figure 11 C(3)) each are made of two pieces of firm elastic goring 6 inches wide and approximately 7 inches long placed one above the other. The two pieces overlap about 2 inches in the center, which gives greater support to the front center. The lower piece of goring on either side is set diagonally downward towards the front, exerting therefore an upward lift rather than a straight posterior pull.

The uplift strap (figure 11 C(4)) is a combination of elastic and non-elastic material. The front forked section consists of firm elastic webbing $1\frac{1}{2}$ inches wide. The latter extends to a buckle located toward the top of the supporter just back of the hips, allowing tightening or loosening of the strap as desired. The uplift straps, being placed diagonally, exert a supporting rather than a suppressing pressure on the lower abdomen.

The belt is fastened in front by means of six skate-buckles and hooks (figure 11 B(2)). The buckles are slipped over the hooks with the straps loose, each may then be individually tightened to the desired degree. The extra length of strap is held up by slots at the origin, rather than allowed to dangle.

Figure 11 A shows the measurements required in making up a belt when the patient is not able to be fitted personally. The measurement for the upper edge of the belt is taken around the body about 1 inch above the anterosuperior spine of the ilium. The measurement for the middle of the belt should pass over the largest part of the abdomen. The measurement for the lower edge should follow the lowest line of the abdomen in front, and cross the spine in back three or four inches below the upper measurement.

The dimensions of a size-40 belt are approximately as follows:

1 *Back* $16\frac{1}{2}$ inches long at the top and 18 inches at the bottom, with three double pieces of whalebone $4\frac{1}{2}$ inches apart. Height is $8\frac{1}{2}$ inches.

2 *Elastic side-sections* 6 inches long made of two pieces of goring 5 inches wide with $2\frac{1}{2}$ inches' overlap, giving a height of 8 inches.

3 *Uplift strap*, the elastic arising at the bottom in front 5 inches long, continued by a web-strap $6\frac{1}{2}$ inches long, passing through a tightening-buckle and inserted into the beginning of the back-piece 2 inches below the top.

4 *Front sections* $2\frac{1}{2}$ inches wide and $9\frac{1}{2}$ inches high, the tongue 6 inches long.

It should be stated that these measurements do not designate the contouring necessary for proper fitting to the body, nor do they take into account the extra length required for seams, etc. They were taken from a finished product, laid flat.

Patients are taught to apply the belt before arising in the morning, preferably outside the undershirt. If a union-suit is worn, the belt can be worn underneath it over a thin garment. The patient should be in the supine position when putting on the belt, and the belt should be tightened from below upward. This is important in order to move the abdominal fat and viscera upward, rather than to compress it in the lower abdomen.

The unusual feature of the belt is the width and height of the elastic side-sections, particularly the width. This is obtained by making the front narrow, permitting the elastic side-sections to extend farther forward on the abdomen where the elasticity is much more beneficial than if it were placed toward the back. This increased elasticity permits expansion of the belt during inspiration. This aids, rather than suppresses abdominal breathing, and prevents limiting respiration to the thorax, as is seen in obese states naturally or where a firm, inelastic belt is applied. The increased elasticity also aids in expiration, and overcomes the prolonged expiratory period seen in those patients with depressed diaphragms due to abdominal ptosis or

emphysema The diaphragm more readily assumes the expiratory position, and is ready to descend with the next inspiration There is no decrease in the supportive effect during the inspiratory expansion

Other devices which provide support plus elastic pressure during expiration would serve the same purpose We have used belts made by inserting the elastic materials over the entire abdomen and back, with firmer materials at the sides with almost equal success Such belts in our opinion are more beneficial for relief of symptoms in obstructive emphysema than firm belts of the type used for visceroptosis

v

Fig 12 Postural correction by use of the belt described Figure on left shows position of extreme relaxation before application of belt

It has been our experience that patients who wear the belt when up and about are obliged to stand more erect, they breathe more freely, and are

relieved of orthostatic dyspnea. They may complain of some fullness after meals which can be controlled by loosening the upper straps. However, the belt may indirectly limit the desire to eat to excess although this is not suggested to the patient, advisedly. Since most of the patients are males we have refrained from using the term "corset" to designate this belt. The

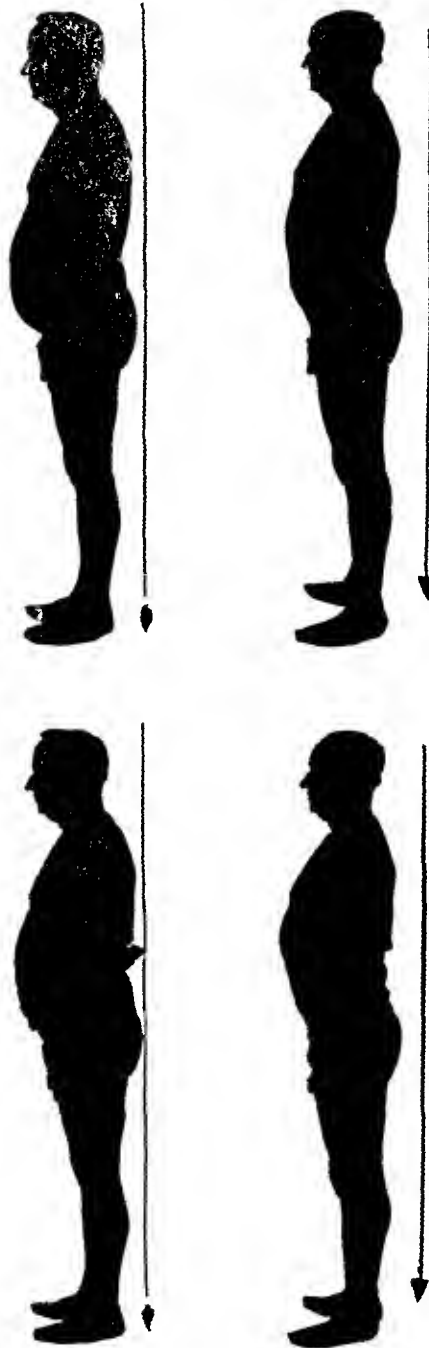


FIG 13 Upper figures without belt lower with belt Left-hand figures made on first visit of patient, right-hand figures taken three months later. It should be emphasized that these are natural poses, no attempt made by the patient to exaggerate his posture.

continued use of the belt is perhaps helpful in removal of fat from the abdominal wall by continuous massage during respiration. Long continued use of the belt may weaken the abdominal muscles, but this result may be minimized by exercises which will be discussed later (figures 12 and 13).

We have observed that the color of patients improves promptly upon use of the belt. The brilliant color associated with the polycythemia diminishes, and cyanosis of the mucous membranes and nails is less striking. We have not followed a large enough series of patients long enough to secure accurate controls of the degree of polycythemia after treatment.

2 Reduction in Weight The plan for reduction in weight must be individualized for each patient, depending upon occupation, opportunity for exercise and general physical condition. A caloric intake should be determined which may be as low as 800 to 1000 calories for some patients. At first two or three pounds per week may be lost and later not more than one or two pounds per week until the patient approaches the ideal weight after a period of six months. In some of these patients the problem of dietary intake is a difficult one, as all who have treated obesity can testify. For the great majority, however, the severity of their previous disability, and the remarkable relief derived by use of the belt give them confidence in measures directed toward the source of their trouble. A silhouette of themselves from the side before treatment will often be a great stimulus for cooperation. The lessening of the girth due to loss of fat and improved posture will also lend encouragement.

3 Postural Exercises Chief among the postural exercises are those which educate the patient to stand properly until the postural reflexes assume command. This requires attention toward the correction of the position of relaxation. Patients should periodically stand with their backs to the wall touching the wall at as many points as possible. When some of the excess weight has been removed, the abdominal muscles may be strengthened by graduated exercises. The familiar admonition to "suck up the guts" employed by instructors in physical education may be very easy to accomplish by boys in their early years, but is almost impossible for the obese.

SUMMARY

The postural syndrome which begins with obesity in the relaxed type of individual and passes through a series of events with increasing protuberance of the abdomen and deformity of the spine, is discussed. The results of continued strain on the spinal axis and irritation of the spinal nerves are manifested by diverse clinical symptoms and signs which frequently bring the patient to specialists in many branches of medicine. The later complications in the abdominal wall, such as herniae, may be classed as "blow-outs" resulting from weakness of the retaining structures. The respiratory and circulatory manifestations are primarily due to interference with proper ventila-

tion of the lungs based upon postural defects and the disadvantages under which the diaphragm functions under the circumstances. The orthostatic dyspnea, reduced vital capacity and tidal air, polycythemia and cyanosis are closely related. In older subjects hypertension, systemic and pulmonary, and arteriosclerosis account for definite cardiac complications. Treatment requires temporary support for the pendulous abdomen and assistance in the evacuation of the lungs during expiration. A belt which gives this support and aids in expiration through the elastic force of materials inserted in the sides of the belt, is described. This we have found of great benefit in the early months of treatment. The weight should be gradually reduced to correct the distortion of the spinal axis and restore the spinal curvature. Postural training is of greater value after the adipose tissue has been reduced, but is of little value in the patient with a pendulous abdomen and a great counterweight of visceral fat which interferes with the ascent of the diaphragm during expiration.

CONCLUSIONS

The postural syndrome beginning with obesity leading to postural pulmonary emphysema and spinal-curve distortion is described, and measures are suggested for treatment which, in our hands, have been of value.

We wish to express our appreciation to Dr John B DeC M Saunders for his suggestions and helpful criticisms.

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EMPHYSEMA REBREATHING, BASAL METABOLIC RATE DETERMINATIONS, VITAL CAPACITY

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THE classical picture of pulmonary emphysema is accepted without question by physicians, pathologists and roentgenologists. The chest is barrel-shaped and remains in the position of inspiration—moves as a whole—with diminished expansion and calls into play the accessory muscles of respiration. The percussion note is hyperresonant with obliteration of the compensatory spaces and the breath sounds are soft and expiration prolonged and sighing. The descent of the bases may be diminished, abdominal breathing is increased, although in long, narrow-chested individuals the diaphragms may descend freely. The lungs at autopsy are pale and voluminous, do not collapse on standing and microscopically present dilated alveoli and infundibular passages, the walls of which are often ruptured, forming unusually large bullae. The elastic tissue of the lungs is broken and the smooth muscle of the bronchioles and air passages degenerated. There is often accompanying chronic inflammatory reaction with formation of fibrous tissue, and some writers even consider pulmonary fibrosis the forerunner and constant companion of pulmonary emphysema.

Until the etiologic factors are more clearly determined pure pulmonary emphysema (not acute, or compensatory, or senile) will remain a theoretical condition and will differ with each hypothesis. There is, for instance, the large school of thought which considers changes in the chest wall and spinal column responsible for the changes in the lung known as emphysema. Another, perhaps larger, school looks on the changes in the chest wall as secondary to the lung changes and caused by the effort, doomed to failure, to compensate by over distention for the innate inadequacy of the lung tissue. A third school¹ attempts to differentiate between two types of emphysema, (a) that which occurs from changes in the chest wall—*postural emphysema*, and (b) that which occurs from some form of bronchial obstruction—*obstructive emphysema*. The postural type—actually one form of senile emphysema—is associated with little or no impairment of respiratory function, since abdominal breathing manages to expand the lungs by increased diaphragmatic expansion and compensates for the functional disability of the chest wall. Obstructive emphysema is accompanied by dyspnea, often extreme, and it has recently been shown² that difficulty in breathing is exaggerated by imperfect use of the respiratory muscles and great improvement can be brought about by suitable muscle training.

We have remaining, then, after eliminating acute, compensatory, senile

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and postural emphysema, a small group of cases of true emphysema of the so-called obstructive type. These occur frequently as a result of asthma or pulmonary fibrosis with or without bronchitis and almost always after long continued coughing. It will not profit us to discuss whether inspiratory or expiratory obstruction is important, or whether repeated localized infections cause compensatory emphysema elsewhere in the lung,³ which may become permanent, or whether hereditary tendency to degeneration of the pulmonary stroma is necessary. These and other points must be established if emphysema is to be prevented, but that time is not yet.

Now, although the clinical picture of emphysema, as I have said, seems to be clear and definite and is accepted as a matter of course, there actually exists much difficulty in ascertaining whether we are dealing with lungs which are merely hyper-resonant and distended but functionally efficient (postural), or whether true functional and pathologic (obstructive) emphysema exists. The fluoroscopic and roentgenographic criteria of emphysema fail in the same manner as do physical signs to provide reliable information, although the careful studies of Fray⁴ have improved this method of examination. With McCann, he has shown that measurements on the roentgen-ray film of the total area of the fully expanded chest when multiplied by the anteroposterior diameter of the patient's chest provides a figure which correlates excellently with total capacity of the lungs in normal young adults. By this method the expected vital capacity of an individual can be estimated and thus a calculated normal established.

The chemical changes which accompany emphysema are well known and recently have been carefully surveyed by McCann et al.⁵ These changes are thought by inference to be brought about by poor mixing of alveolar air and diminished and defective alveolar surface. The alveolar CO_2 is increased and the arterial CO_2 content is increased, the arterial oxygen content is reduced and there is an increased tolerance for high CO_2 tension in respired air.

The total lung volume, as estimated by Christie's⁶ oxygen dilution method, remains essentially unchanged, but vital capacity is reduced at the expense of complementary air and residual air is increased. McCann⁷ finds that when residual air is over 40 per cent of total capacity some degree of anoxemia exists and anoxemia increases more or less proportionally to the increase in the residual air. It has been assumed that an increase in residual air and decrease in vital capacity cause inefficient alveolar ventilation, which in turn leads to diminished oxygen saturation of the arterial blood. Either of these estimations (i.e., residual air or oxygen unsaturation of arterial blood) is closely correlated with dyspnea and is thought to afford a fair index of pulmonary efficiency. It seems clear, however, that neither one expresses an accurate measure of potential pulmonary efficiency for any given individual.

The elastic recoil of the lung is lost or impaired as shown by its failure

to collapse on opening the chest at autopsy and by reduction during life of the negative intrapleural pressure (Christie⁸) It has been suggested⁹ that the principal factor in the loss of power to recoil is not damage to the elastic tissue of the lung but is reduction of the surface tension of the layer of moisture lining the overdistended alveoli Correlation of loss of elastic recoil of the lung with functional respiratory impairment obviously is not available for clinical purposes

The symptoms produced by emphysema are usually thought of as those caused by deficient oxygenation of the blood during its passage through the lung and are mainly dyspnea and cyanosis with late cardiac manifestations and occasionally secondary polycythemia

In the course of subjecting a patient suspected of having angina pectoris to the rebreathing test devised by Baker¹⁰ I was struck by the amount of dyspnea and cyanosis produced in the patient at the end of two minutes, whereas an average individual can continue the test for five to seven minutes with little or no discomfort The test consists of partially filling a Benedict-Roth metabolism apparatus with room air, leaving the soda lime in the apparatus as usual, and allowing the patient to rebreathe into the closed system, thereby gradually removing the oxygen and providing a steadily lessening oxygen mixture, thus producing an increasing anoxemia Patients with angina pectoris usually experience cardiac pain in the course of four to six minutes, but rarely complain of dyspnea The patient was a man of 40 years whose complaint was substernal distress and dyspnea on exertion There were no signs of cardiac failure except dyspnea on exertion and he had the classical physical findings of pulmonary emphysema After the patient had returned to Florida it was borne in on me that this test might be used as a gauge of functional respiratory reserve Since that time I have tested by this method 18 other cases that presented various degrees of clinical emphysema, but in no other case has there been any evidence of increased susceptibility to reduced oxygen tension I am at a loss to explain its occurrence in the first individual It seems possible that the increased residual air which is present in cases of emphysema contains more total oxygen than exists in normal residual air and thus allows the rebreathing test to continue for an abnormally long time before producing noticeable dyspnea or cyanosis In any event rebreathing air in which the percentage of oxygen is constantly being reduced does not offer a means of diagnosing and measuring functional impairment of the lungs in emphysema

Observations on the basal metabolic rate were made in the usual manner by filling the cylinder once with oxygen and once also with room air It is interesting to note that there was no appreciable difference in withdrawal of oxygen from the closed system whether offered in room air or in a mixture approximating pure oxygen (figure 1) One may surmise from this observation that the usual method of determining the basal metabolic rate in patients with emphysema is accurate and not vitiated by the existence of

oxygen unsaturation of the arterial blood which is known to exist. Here again the large amount of residual air probably acts as a buffer to prevent unusually rapid absorption of oxygen. Actual observations on arterial oxygen unsaturation before and after each method are necessary to afford

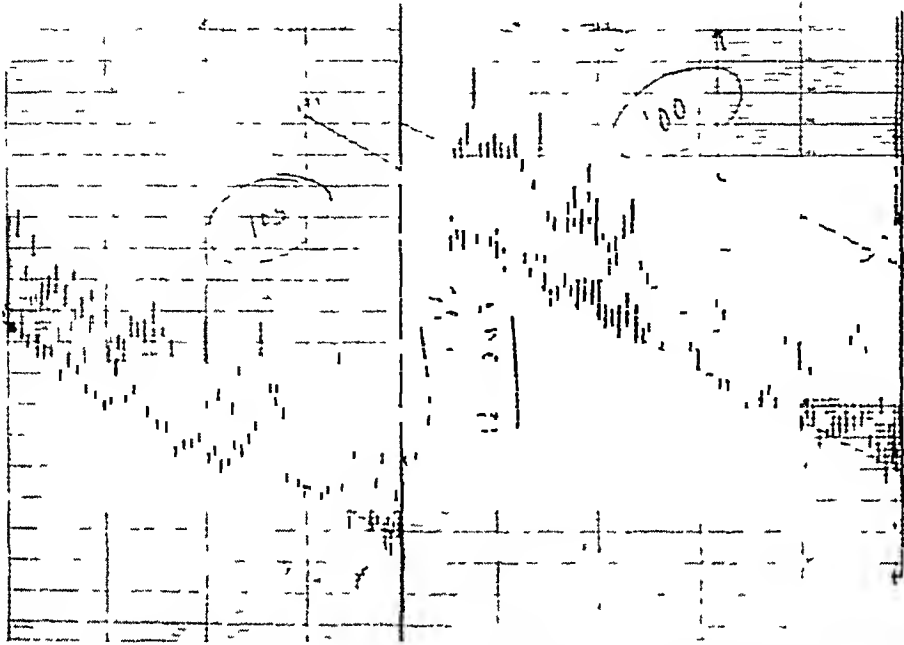


FIG 1 Rebreathing test on a patient with advanced emphysema. The first curve represents the amount of oxygen withdrawn from room air and the second curve the amount withdrawn from pure oxygen approximately an equal amount.

conclusive evidence on this point and these were made in only one case which showed the characteristic changes.

Finally the graphic method of recording vital capacity was added to these observations and certain variations from the normal curves were noted. In using the Benedict-Roth apparatus 20.73 c.c. of gas will raise the spirometer bell 1 mm. and the vital capacity may easily be determined by measuring on the graph in millimeters the extent of deep inspiration and forced expiration and multiplying this figure by 20.73. This method also allows vital capacity to be divided into reserve, tidal and complemental air. Without exception the vital capacity of patients suffering from clinical emphysema is reduced.

Christie has pointed out that after deep inspiration patients with emphysema are unable to blow out as much reserve air as they can after a normal inspiration (figure 2). McCann confirmed this finding in some cases but not in others, and reproduced a curve from one patient in whom the complemental air was greatly reduced and the reserve air normal or increased. A factor which seems to have been overlooked in this test is the amount of CO_2 which is absorbed by soda lime during expiration. Following inspiration after the dead space (150 c.c. to 200 c.c.) has been washed

out the expired air contains 6 to 7 per cent of CO_2 , all of which is removed from the gas in the metabolism apparatus by the soda lime, causing a false lessening of the vital capacity and this false lessening appears on the graph as a shortening of the end of the downward arm which usually registers re-

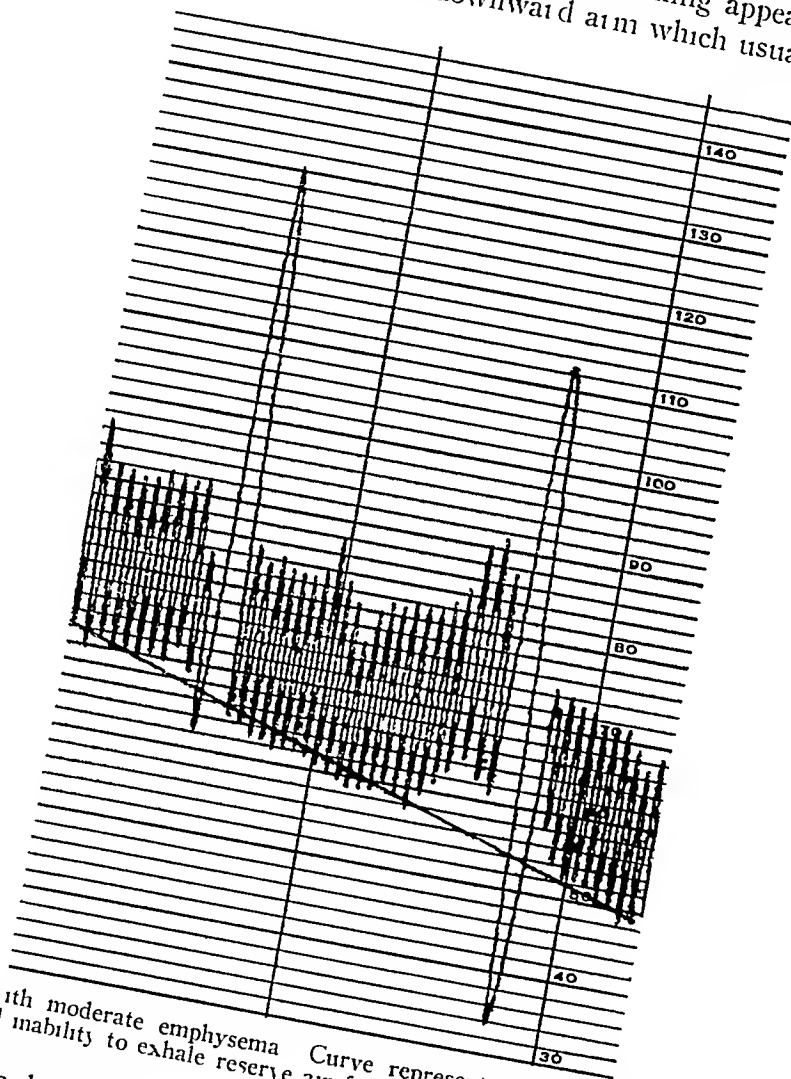


FIG 2 Patient with moderate emphysema. Curve represents reduction in vital capacity and inability to exhale reserve air following deep inspiration.

serve air. This lessening occurs in normal individuals also. The true figure for vital capacity is more nearly approximated by starting with forced expiration after a normal inspiration and then measuring the amount of air inhaled by forced inspiration (figure 3).

From my tracings it was also noted that when breathing normally after a deep inspiration the former resting phase was reached only after 8 to 20 breaths (figure 3). I believe both of these changes are due to inefficient use of the chest wall and faulty habits of breathing rather than to the loss of pulmonary elasticity as has been previously hypothesized.

There is no reason to believe that the lung would shrink further from a partially distended state than it would from a fully distended one. Expiration is a passive movement during quiet breathing and becomes active only during dyspneic breathing. In a normal person, with normal chest wall-

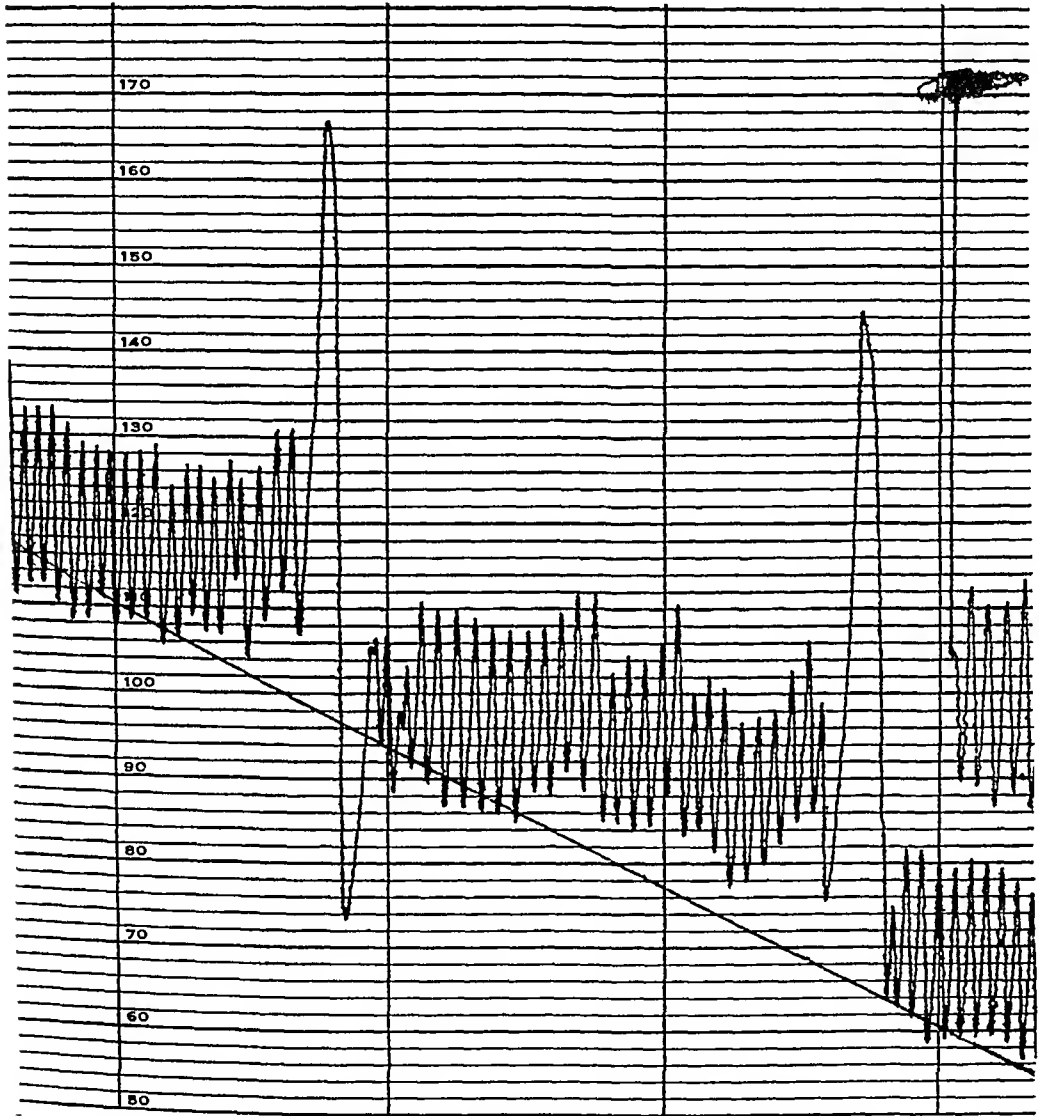


FIG 3 Patient with extreme emphysema. Vital capacity is greater when test is begun with expiration. Former resting point is slowly regained after forced inspiration.

lung breathing mechanism, need for greater respiratory activity is supplied by more rapid ventilation of a normal or temporarily slightly increased residual air. This is done by larger inspiratory movement followed by an associated active expiratory movement with the result that the proportion of tidal air to residual air is increased. In other words the life long habit of response to the need for more rapid ventilation of the lungs is an increased inspiratory effort with only a secondarily increased expiratory effort.

When, for whatever reason, residual air is permanently increased as it is in emphysema, tidal air is constantly increased to maintain the required residual air/tidal air proportion. This increase in tidal air on top, as it were, of an increased residual air encroaches on complementary air and brings about breathing at a higher and less efficient resting point. The larger residual

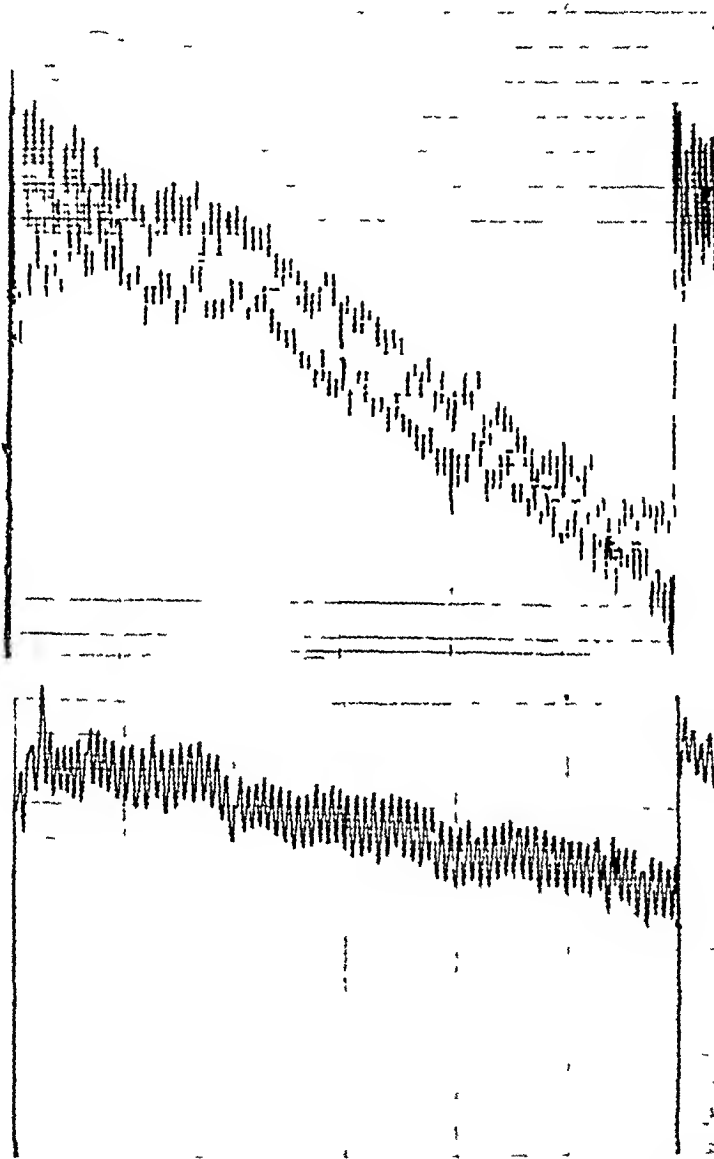


FIG 4 Basal metabolic rate determinations before (above) and after (below) subtotal thyroidectomy. Respiratory rate is practically the same in the two tests whereas tidal air is increased in the hyper- and decreased in the hypothyroid state.

air could be more rapidly ventilated when need be if tidal air could be increased partially at the expense of residual air but the life long unconscious training of forced breathing is in the direction of voluntarily increasing

inspiration and allowing expiration automatically to keep pace. In patients with emphysema the act of forced expiration is unable to keep pace with forced inspiration as is seen in figures 2 and 3. Reserve air can be expired only when forced expiration starts from the top of tidal air, that is, from the end of a normal unforced inspiration. For this reason in our clinic we are training emphysema patients to start the respiratory cycle with forced expiration and to allow inspiration to take care of itself. It is too early to report the results of this practice but temporarily improved breathing has been noted.

Studies of tracings made during basal metabolic rate determinations of patients before and after treatment for hyperthyroidism (figure 4) in individuals possessing a normal respiratory apparatus reveal that tidal air is increased in the hyper- and reduced in the hypothyroid state while the respiratory rate remains the same. However, it has long been known (Peabody¹²) that vital capacity is reduced in hyperthyroidism and in like manner the residual air recently has been reported (Robb and Weiss¹³) to be increased in hyperthyroidism and to diminish with improvement in the condition. It is evident, then, that changes in the subdivisions of total pulmonary capacity may depend on functional requirements and need not predicate structural change. Similar changes have been found in patients suffering from congestive heart failure and to this state in these, as well as in patients suffering from hyperthyroidism, the term "functional emphysema" has been applied. This term has been evolved to express the similarity of changes occurring in the subdivisions of total pulmonary capacity in cases of emphysema on the one hand and hyperthyroidism and congestive failure on the other. An effort has been made to carry the similarity further and to describe changes in alveolar blood volume which would reduce the elasticity of, and stiffen, the pulmonary tissue and in this and other ways reduce pulmonary efficiency in a manner similar to emphysema. In the hyperthyroid patient however, we know that the lung is adequately supplying an increased body oxygen requirement. Is it not reasonable to suppose that an augmented residual air which is properly ventilated by increased tidal air offers a simple way of meeting an increased oxygen demand? That these patients are dyspneic on exertion may be explained by the elevated resting point which in turn necessitates overextension of the chest early in the process of overventilating, but this tendency to dyspnea does not indicate that the respiratory apparatus is not functioning unusually well while the patient is at rest. Seen in this light the condition hitherto alluded to as "functional emphysema" might now be considered as a normal response to an increased demand for oxygen. It seems fair to inquire whether certain changes noted in emphysema patients also may not depend on functional requirements rather than changes in the lung parenchyma.

CONCLUSIONS

1 Rebreathing air containing a gradually diminishing oxygen percentage has not been shown to serve as a test for respiratory functional disability in patients thought to have clinical evidence of emphysema

2 Basal metabolic rate determinations in patients with emphysema seem to yield reliable results

3 It is important to realize that increase in residual air may constitute one factor in a method of increasing oxygenation of the blood and should not be accepted per se as evidence of reduced pulmonary efficiency

4 The term "functional emphysema" should not be used since it implies knowledge of emphysema not yet available and may lead to false hypotheses

5 Reeducation in breathing offers symptomatic improvement to patients suffering from emphysema

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CLINICAL STUDIES ON VERODIGEN, A DIGITALIS GLUCOSIDE

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VERODIGEN, a gitalin-like fraction of digitalis, has been used for a number of years in several European countries, and in some instances has largely replaced the galenical preparations of digitalis. There have been a number of reports on its usefulness,^{1 2 3} which give the impression that it is considered superior to digitalis in several ways. From a clinical standpoint it is said to be absorbed more readily and to exert its effect on the heart more rapidly than digitalis. It is claimed, moreover, that this drug is borne by the gastrointestinal tract better, causing nausea and vomiting less often than digitalis.

In this country, Verodigen has been used but a few years. Stroud et al⁴ conducted both pharmacological and clinical studies, finding the qualitative effects of Verodigen to be the same as those of digitalis leaf. By biological assays they found the drug to be 130 times as potent as digitalis, and clinically, to be 360 times as strong—i e, 1/240 gr of Verodigen was found to be equivalent to 1.5 gr of digitalis leaf. These investigators were able to secure complete digitalization with from 1/10 to 1/16 gr, given over a period of five to six days.

In our study, we have used Verodigen on unselected cases of congestive heart failure, both those showing a normal sinus rhythm and those with auricular fibrillation. The group of cases studied in the hospital were kept in bed at conditions as nearly uniform as possible until compensation was restored. In the great majority of cases, no other drugs than occasional sedatives and opiates were used. The ambulatory cases were examined at the out-patient department about once every week. None of these cases had received other digitalis preparations for at least a month before the beginning of Verodigen.

Brief histories of the cases studied in the hospital follow. Table 1 gives the essential features in these cases on admission to the hospital (top line) and after the maximum therapeutic effects had been obtained with Verodigen (bottom line). In those cases showing auricular fibrillation the apical and radial rates are separated by colons.

ABSTRACT OF HOSPITAL CASES

D 1, a 41 year old colored male, on admission to the hospital (4/22/35) complained of shortness of breath on exertion for two or three months and swelling of

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TABLE I

Case	Age Years	Sex	Etiologic Classification	Congestive Failure	Weight	Blood Pressure	Pulse	Vital Capacity	Total Verodigen Necessary for Digi- talization, Days Administered
D T	41	M	Arteriosclerosis	+++ 0	243	170/120	98	1600	11/80
G J	47	M	Arteriosclerosis	++	203	140/75	70	3200	4
W G	36	M	Syphilis	++	122	170/115	128	1600	6/80
H L	49	M	Unknown	+++	121	130/88	76	3300	3
E W	52	F	Unknown	++	149	160/60	102	?	6/80
J M	52	M	Arteriosclerosis	+++ 0	—	160/56	76	1800	3
Jos M	52	M	Arteriosclerosis	+++	190	125/105	100	1100	6/80
W M	43	M	Arteriosclerosis	++	—	120/80	84	2600	2
R D	60	M	Arteriosclerosis	+++	148	160/110	120	1100	8/80
A P	64	F	Arteriosclerosis	++	126	130/85	70	2300	3
C M	56	F	Unknown	++	170	136/70	126	?	14/80*
J H	48	M	Arteriosclerosis	++	142	216/156	76	2000	6
				0	176	190/130	114	1250	9/80
				++	161	216/130	72	2700	5
				++	130	165/100	108	1700	9/80
				0	125	180/100	80	2500	3
				+++	140	160/92	100	—	12/80
				+++	—	170/104	72	—	8
				++	—	150/80	164	—	7/80
				0	—	180/112	104	1400	2
				+++	112	170/90	150	1600	12/80†
				0	105	168/105	80	—	5
				++	—	140/80	128	—	8/80
				++	—	—	80	—	3
				++	—	—	80	2300	8/80

* Lost some by vomiting on second day Developed extrasystoles sixth day
† Lost some by vomiting on first and second days

the ankles for two months. He had continued at work until three weeks prior to admission, when he became too dyspneic. During the past week, edema gradually involved the legs, thighs, scrotum and penis. He had some bloody expectoration four days before admission.

Physical examination revealed marked orthopnea and engorgement of the neck veins. The apex of the heart, in the fifth interspace, extended to the anterior axillary line. Heart sounds were distant. A systolic murmur was audible at the apex. Occasional runs of extrasystoles interrupted an otherwise normal rhythm, the rate being 98. Blood pressure 170 systolic and 130 diastolic. The lungs showed moist râles over both bases with flatness to percussion over the right base. The liver was palpable well below the costal margin, and a fluid wave could be elicited in the abdomen. The sacrum, genitalia and extremities showed marked pitting edema. A seven-foot roentgenogram showed a transverse diameter of the heart of 21.2 cm and of the thorax of 34.6 cm.

Laboratory studies: slight anemia, urine—albumin, trace; occasional red and white blood cells and hyaline and granular casts, Wassermann + plus.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement, myocardial fibrosis
- C Regular sinus rhythm
- D Class III

On the evening of admission, Verodigen was started and a total of 11/80 gr was given in the next three days. During this time the pulse gradually fell to 80 (subsequently to 70), the vital capacity increased to 2300 cc (three days later to 3200 cc), râles in chest, enlarged liver and peripheral edema cleared up entirely, and there was marked diuresis. It is not to be thought that Verodigen was wholly responsible for the weight loss and diuresis, for 1 cc of Salyrgan was given on three successive days.

G J, a 47 year old colored male, was admitted to the hospital 4/13/35 with a history of two spells of breathlessness, 14 and 11 months previously, both of which had been relieved by some medicine prescribed by his family physician. Three weeks prior to admission, breathlessness returned, as well as several mild attacks of nocturnal dyspnea. Orthopnea had been present in the past few weeks. No history of edema. A past history was given of "bad blood" 12 years ago, for which he received 20 injections in the arm.

On physical examination he appeared slightly dyspneic and orthopneic. The neck veins were not distended. The apex beat of the heart was in the fifth interspace at the mid-clavicular line. There was a systolic murmur at the apex and a markedly accentuated, amphoric pulmonic second sound. The rhythm was regular, the pulse 128, blood pressure 170 systolic and 115 diastolic. The lungs showed numerous moist râles over both bases. There was no enlargement of the liver or peripheral edema. A seven-foot roentgenogram of the chest showed the transverse heart shadow to be 14.6 cm, of the chest 27.9 cm.

Laboratory studies: urine and blood essentially negative. Wassermann negative.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement
- C Regular sinus rhythm
- D Class II b

Verodigen administration was begun the day of admission, a total of 6/80 gr being given in three days. At the end of this time the pulse had dropped to 80, orthopnea and râles had cleared up and other changes taken place as shown in table 1.

He was continued on a daily dose of 1/240 gr Verodigen until and after discharge on 4/20/35

W G, a colored male, 36 years old, was admitted to the hospital 4/17/35, complaining that nine months previously he had begun having a feeling of fullness in the chest and attacks of paroxysmal dyspnea, especially at night. About the same time he began having a troublesome cough, nocturia and some swelling of the feet. Six months ago he took some heart medicine prescribed by his family physician which did not relieve him much so he has taken none for the past three months. Inquiry into his past history revealed the fact that he took eight injections "for his blood" two years ago, and that he was operated on for an ischio-rectal abscess in 1932.

On physical examination he showed slight engorgement of the neck veins. His heart was enlarged, the apex beat being 14 cm from the mid-sternal line in the sixth interspace. There was a prolonged diastolic murmur heard over the aortic area and systolic murmur over the apex and aortic area. The rhythm was suggestive of gallop, rate 120. Blood pressure was 160 systolic and 60 diastolic. Moist râles could be heard over the bases of both lungs. The liver edge was palpable and there was moderate pitting edema of the ankles. A seven-foot roentgenogram of the chest showed the transverse heart shadow to measure 19.6 cm, the chest 29.2 cm.

Laboratory studies: urine essentially negative. Blood showed moderate anemia. Wassermann 4 plus.

Cardiovascular diagnosis

- A Syphilis
- B Cardiac enlargement, aortic insufficiency
- C Regular sinus rhythm
- D Class II a

He received 5/80 gr Verodigen the day of admission with a fall in pulse rate to 80, and 1/80 gr the day after admission, following which his pulse rate dropped to 76 and remained at that level. He was given a maintenance dose of 1/240 gr daily. Within four days, all signs of congestive failure had cleared up.

H L, a 49 year old colored man, was admitted to the hospital 4/23/35 with a history of having caught cold and begun to cough three weeks previously. Following this he developed marked breathlessness and orthopnea. He had had nocturia three to four times since onset of present illness. Nine years ago he had both legs amputated above the ankles on account of frost bite.

Physical examination revealed marked orthopnea and slight engorgement of the neck veins. The heart was slightly enlarged, the apex beat being just outside the mid-clavicular line in the fifth interspace. There was a systolic murmur at the apex and an accentuated P. The rhythm was normal, rate 100. Blood pressure was 125 systolic and 105 diastolic in both arms. The chest was emphysematous in type, and there were dullness and râles over both bases. The liver edge was palpable four fingers below the costal margin, and there was moderate pitting edema of the abdominal wall and over the sacral region. Both legs had been amputated about the middle of the tibiae. A seven-foot roentgenogram of the chest showed the transverse diameter of the heart to be 18.1 cm, of the chest 30.6 cm.

Laboratory: urine and blood essentially negative. Wassermann 4 plus.

Cardiovascular diagnosis

- A Unknown
- B Cardiac enlargement
- C Regular sinus rhythm
- D Class III

On the day following admission he was started on Verodigen and received 8/80 gr in the space of three days. During this time his pulse rate dropped to 84, and

signs of congestive failure showed considerable clearing, within two more days they had disappeared altogether. He was given a maintenance dose of 1/240 gr and remained comfortable.

E W, a 52 year old white woman, was admitted to the hospital 5/14/35 complaining of paroxysms of dyspnea accompanied by cough, which had begun 15 months previously. These symptoms were much worse when lying down. In the past few days she has noticed swelling of the ankles.

Physical examination revealed an obese woman quite orthopneic, with neck veins markedly engorged. The heart was enlarged beyond the mid-clavicular line, the extent being impossible to judge on account of her obesity. The rhythm was suggestive of a gallop type, rate 120. Blood pressure 160 systolic and 110 diastolic. Asthmatic breathing could be heard over the upper chest, and numerous moist râles over the bases. The liver was palpable and ascites present. There was moderate pitting edema over the ankles. A seven-foot roentgenogram of the chest showed the transverse diameter of the heart to be 19.7 cm, of the chest 27 cm.

Laboratory studies unimportant.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement, myocardial fibrosis
- C Regular sinus rhythm
- D Class III

The administration of Verodigen was begun the day of admission and a total of 14/80 gr given in six days. Vomiting on the second day probably excluded 1/80 or 2/80 gr. During this time the heart rate slowed to 70, and practically all signs of congestive failure cleared up. On the sixth day extrasystoles were observed clinically and electrocardiographically, but there were no other signs of over-dosage. The drug was withdrawn for four days, following which the pulse ranged from 80 to 84. She was discharged on a maintenance dosage of 1/240 gr.

J M, a 52 year old colored man, was admitted to the hospital 7/17/35 with a history of dyspnea on exertion for the past four weeks with progressive swelling of the lower extremities. During this time he suffered with orthopnea and occasional attacks of paroxysmal nocturnal dyspnea. During the past week he has had a non-productive cough and dull aching pain over the heart. No previous history of decompensation.

On physical examination he was seen to be orthopneic, with marked engorgement of the neck veins. The apex beat of the heart was in the sixth interspace at the anterior axillary line. The rhythm was grossly irregular, the apical rate 126, radial 76, blood pressure 170 systolic and 86 diastolic. Peripheral arteries were tortuous and sclerosed. The lungs showed moist râles over both bases. The liver extended down almost to the umbilicus and there was pitting edema as high as the knees. A seven-foot roentgenogram of the chest showed the transverse diameter of the heart to be 23.8 cm, of the chest 32.2 cm.

Laboratory urine and blood essentially negative. Wassermann 4 plus.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement
- C Auricular fibrillation, established
- D Class III

Verodigen administration was begun the day of admission, 9/80 gr being given in four days, and 1/240 gr daily thereafter. There was a progressive improvement in symptoms and physical signs, coincident with a slowing of the ventricular rate and decrease in the pulse deficit. Within eight days all signs of decompensation had disappeared, and he was discharged later on a daily dose of 1/240 gr Verodigen.

Jos M, a 43 year old colored man, was admitted to the hospital 8/11/35 complaining of dyspnea on exertion for the past two months. He had to stop work three weeks ago since when his dyspnea has become progressively worse. A productive cough and nocturnal dyspnea have been troublesome features. Recently his feet and ankles have begun to swell.

Physical examination revealed moderate engorgement of the neck veins. The apex beat was 14.5 cm from the mid-sternal line in the fifth interspace. The rhythm was normal, rate 114. Blood pressure 216 systolic and 156 diastolic. The lungs showed moist râles over the bases and musical râles throughout. The liver was palpated 5 to 6 cm below the costal margin. There was pitting edema over the sacrum and of the extremities as high as the thighs. A seven-foot roentgenogram showed the transverse diameter of the heart to be 17.3 cm, of the chest 29.1 cm.

Laboratory urine showed a slight trace of albumin and rare hyaline casts. Blood showed moderate secondary anemia. Wassermann negative.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement
- C Regular sinus rhythm
- D Class III

Verodigen administration was begun the day following admission and a total of 9/80 gr given in three days following which 1/240 gr was given daily. During this time the heart rate slowed to 68 and all signs of congestive failure cleared up. The diuresis and loss of weight in this case were due largely to the use of Salyrgan.

W M, a 60 year old colored man, was admitted to the hospital 8/9/35. For the past four months he has suffered with dyspnea on exertion, which has grown steadily worse. Three weeks ago his feet and ankles began to swell. For the past two weeks he has had frequent attacks of paroxysmal nocturnal dyspnea.

Physical examination revealed slight engorgement of the neck veins. The apex beat was 16 cm from the mid-sternal line in the sixth interspace. The rhythm was normal, rate 108. Blood pressure 216 systolic and 100 diastolic. There was marked sclerosis of the peripheral arteries. Musical and sibilant râles could be heard over both lungs, most marked over the bases. The liver was not palpable, but the extremities showed pitting edema as high as the knees. A seven-foot roentgenogram showed the transverse diameter of the heart to be 18 cm, of the chest 27.9 cm.

Laboratory urine and blood essentially negative. Wassermann negative.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement, myocardial fibrosis
- C Regular sinus rhythm
- D Class II b

The administration of Verodigen was begun the day of admission and a total of 12/80 gr given over a period of eight days, with a fall in pulse rate to 80 and a simultaneous clearing of the signs of decompensation. In this case diuresis and weight loss can be attributed largely to Verodigen for no diuretics were given.

R D, a 64 year old colored female, was admitted to the hospital 9/8/35. She gave a history of dyspnea on exertion and occasional mild attacks of paroxysmal dyspnea for one month prior to admission. She had also had a non-productive cough, edema of the right ankle and nocturia. She had a severe attack of paroxysmal dyspnea just before admission, which caused her to seek hospitalization. Past history negative for cardiac symptoms and anti-syphilitic treatment.

Physical examination, after relief of the immediate attack by morphia, revealed orthopnea and moderate engorgement of the neck veins. The apex beat of the heart

was felt in the sixth interspace at the anterior axillary line. A systolic murmur was audible over the apex. Frequent extrasystoles were present. Pulse 110. Blood pressure 220 systolic and 116 diastolic. There were numerous moist râles over the bases of the lungs. The liver was palpable 3 to 4 cm below the costal margin, and there was slight pitting edema of the ankles. A seven-foot roentgenogram showed the transverse diameter of the heart to measure 17.9 cm, of the thorax 24.6 cm. A large saccular area extended from the ascending aorta, thought to be aneurysm (confirmed later by fluoroscopy).

Laboratory. Blood—moderate anemia, urine—essentially negative. Blood Wassermann and spinal fluid Wassermann negative.

Cardiovascular diagnosis

- A Unknown
- B Aneurysm of ascending aorta, cardiac enlargement
- C Premature ventricular contractions
- D Class III

Verodigen administration was begun the day after admission, a total of 7/80 gr being given in two days, at the end of which time the pulse rate had fallen to 72, and the signs of decompensation had practically disappeared. She was given a daily maintenance dose of 1/240 gr.

A. P., a 56 year old white woman, was admitted to the hospital 4/11/35. Three weeks before just after going to bed, she had an attack of wheezing and suffocation which forced her to stand erect for some time in order to get her breath. This was accompanied by very rapid heart action. Following this attack she noticed dyspnea and fatigue when attempting to perform her usual duties, but continued working for one week. During this time her feet became markedly swollen. For the two weeks preceding admission she was unable to do anything, and had to sit propped up most of the time. Her past history was negative except for a "nervous breakdown" three years previously.

On examination it was noted that she was markedly orthopneic and that her neck veins were moderately distended. The apex beat was at the anterior axillary line in the sixth interspace. Rhythm was grossly irregular, apical rate 164, radial 142. The blood pressure 170 systolic and 104 diastolic. There was flatness on percussion over the right lung base, and moist râles on both sides, also râles at left apex. The liver was palpable 3 to 4 cm below the costal margin. There was moderate edema of the lower extremities.

Laboratory. Urine and blood essentially negative. Wassermann 4 plus.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement, myocardial fibrosis
- C Auricular fibrillation, established
- D Class III

The administration of Verodigen was begun on the day following admission and a total of 12/80 gr given in five days. The patient vomited several times and some of this drug must have been lost. Of this total 3/80 gr was given by rectum. At the end of this time, her apical rate was 104, radial 100, she was much more comfortable and showed signs of diminution in her congestive failure. At this time however she developed a thrombosis of the right femoral artery, which was removed successfully at operation. Two days later however, she suffered a fatal hemorrhage from this region.

C. M., a 48 year old white man, was admitted to the hospital 5/29/35, having had marked dyspnea and orthopnea for the past week. During this time he also had a troublesome cough. Six months previously he had an illness with swelling of the

abdomen, which his family physician said was an 'enlarged liver due to heart disease'

On physical examination, orthopnea was present, but the neck veins were not distended. The apex beat was 3 cm lateral to the mid-clavicular line in the fifth interspace. Rhythm was normal, rate 150. Blood pressure 180 systolic and 112 diastolic. Moist râles were heard over both lung bases. The liver edge was palpable 4 cm below the costal margin but there was no peripheral edema. A seven-foot roentgenogram showed the transverse diameter of the heart to be 17.4 cm, of the chest 31.7 cm.

Laboratory Urine—heavy trace of albumin occasional granular casts. Blood morphology normal. Wassermann negative.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement
- C Regular sinus rhythm
- D Class II b

The administration of Verodigen was begun the day of admission, and a total of 8/80 gr given in the next three days. During this time the signs of congestive failure cleared rapidly and he was continued on 1/240 gr daily.

J H., a 54 year old white female, was admitted to the hospital 9/28/35. Her present illness began about three months previously, with shortness of breath on exertion. Since that time, she had had symptoms of progressive congestive failure, i.e., dyspnea, orthopnea, attacks of paroxysmal nocturnal dyspnea, edema of lower extremities and swelling of abdomen. She was confined to bed for 10 days. Her past history reveals that she had several attacks of rheumatic fever between the ages of 11 and 20 years. She had had several attacks of congestive failure, all of which had been controlled by digitalis.

On physical examination she showed marked orthopnea and distention of the neck veins. The apex beat was palpable in the fifth interspace 14 cm from the mid-sternal line. There was a diastolic murmur heard best at the apex, followed by a snapping first sound. A loud systolic murmur was also present. The rhythm was grossly irregular, the apical rate being 128, the radial 104. Blood pressure 168 systolic and 105 diastolic. Moist râles were audible over both lower lungs. The liver was enlarged 3 to 4 cm below the costal margin and was quite tender. No evidence of ascites was present. There was pitting edema over the sacral region and the entire lower extremities.

A seven-foot roentgenogram of the chest showed the transverse diameter of the heart to measure 16 cm, of the chest, 26.6 cm.

Laboratory Urine—albumin trace occasional granular casts. Blood slight secondary anemia. Wassermann negative.

Cardiovascular diagnosis

- A Rheumatic fever
- B Cardiac enlargement, mitral stenosis and insufficiency
- C Auricular fibrillation established
- D Class III

Verodigen was begun the day of admission, a total of 8/80 gr being given in three days, at the end of which time all signs of congestive failure had disappeared, and the heart rate had slowed to 80 with no pulse deficit.

Ambulatory patients were followed in the out-patient department of the Medical College of Virginia. None of these cases had been taking digitalis for at least one month prior to starting Verodigen. All of them

SUMMARY OF AMBULATORY PATIENTS FOLLOWED WITH VERODIGEN THERAPY

Case	Age	Sex	Etiologic Classification	Congestive Failure	Blood Pressure	Pulse Rate		Amount Necessary for Digitalization	Maintenance Dose	Period of Observation
						Before	After			
W B	60	M	Arteriosclerosis	++	170/80?	100?	80	6/80 gr	1/240 gr	3 months
J S	56	M	Arteriosclerosis	++	180/120?	130?	90	10/80 gr	1/240 gr	1 month
C G	77	M	Arteriosclerosis	+	180/110	110	70	5/80 gr	1/240 gr	2 months*
G J	47	M	Unknown	+	160/110	90	84	6/80 gr	1/240 gr	5 months
W G	45	M	Syphilis	++	150/40	90	90	6/80 gr	1/240 gr	1 month*
W C	59	M	Arteriosclerosis	++	200/120	110	90	5/80 gr	1/240 gr	2 months*
R T	46	F	Arteriosclerosis	++	180/120	120	85	8/80 gr	1/240 gr	1 month
E B	30	F	Rheum fever	++	170/110?	120?	90	5/80 gr	1/240 gr	1 month
F M	48	M	Arteriosclerosis	++	210/100	105	80	10/80 gr	1/240 gr	2 months
H M	40	M	Arteriosclerosis	++	180/120	110	90	8/80 gr	1/240 gr	1 month

* These patients succumbed during treatment

had some degree of congestive heart failure. Three patients had fibrillating auricles, the others having regular sinus rhythm. Verodigen was administered orally in either 1/80 or 1/240 grain tablets. Each patient was examined at least once every week.

Initial response to Verodigen was excellent, but frequently after the patients began improving, their apparent well being and alleviation of symptoms caused them to discontinue the routine instructions resulting in a return of congestive failure phenomenon. It may be stated unequivocally that after amounts of Verodigen ranging from 8/80 to 10/80 grains, clinical improvement equalling that obtained with digitalis was noted.

ABSTRACT OF AMBULATORY CASES

W B, a white male, aged 60, entered the out-patient department on August 20, 1935 complaining of shortness of breath and swelling of his ankles for the past three months. Physical examination revealed a dyspneic, aged white male with engorgement of his neck veins. The left border of the heart was 2 cm beyond the left nipple line. The rhythm was totally irregular, apical rate 100. Radial rate 80. Blood pressure 170 systolic and 80 diastolic. Moist râles were present in the bases of both lungs. The liver edge was felt 2 cm below the right costal margin. There was moderate peripheral edema.

Verodigen was given in dosage of 1/80 grain every four hours for six doses, followed by 1/240 grains every night. At the end of seven days, the patient showed remarkable clinical improvement. The venous engorgement had subsided, the moisture in the lung bases was negligible, the heart rate was 84, the radial rate was 80, blood pressure 150 systolic and 70 diastolic, the liver edge could just be palpated, and the peripheral edema had lessened. Three months later, the patient appeared fully compensated taking a daily maintenance dose of Verodigen of 1/240 grain.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement, myocardial fibrosis
- C Auricular fibrillation, established
- D Class II b

J L S, a colored male, aged 56, entered the out-patient department on September 3, 1935 complaining of shortness of breath, swelling of his ankles, and nocturia over a period of several months.

Physical examination revealed a dyspneic, moderately edematous, colored male with generalized arteriosclerosis. His neck veins were distended. The heart was moderately enlarged, the rhythm was totally irregular, apical rate 130, radial rate 110, blood pressure 180 systolic and 120 diastolic. There was moisture in both lung bases. The liver edge was palpable at the level of the umbilicus. There was moderate pitting peripheral edema.

Verodigen was given in dosage of 1/80 grain every four hours for 10 doses followed by 1/240 grain every night. At the end of 14 days, the patient was improved. The congestive failure phenomena had lessened, the apical rate was 90, the radial rate was 86, a few moist râles were present in the lung bases, there was moderate peripheral edema. One month later the only sign of decompensation was moderate enlargement of the liver and some edema about the ankles. The radial and apical rate remained about 90.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement
- C Auricular fibrillation, established
- D Class II

C G, a colored male, aged 77, entered the out-patient department on April 25, 1935 complaining of weakness, shortness of breath on exertion, swelling of his ankles, and frequency of urination, over a period of 12 months

Physical examination revealed a dyspneic, old colored male with marked generalized arteriosclerosis. The neck veins were distended. The left border of the heart was in the sixth intercostal space, anterior axillary line. The rhythm was regular. The rate was 110 per minute. There were no murmurs. Blood pressure 185 systolic and 110 diastolic. Moist râles were present in both lung bases. The abdominal wall was edematous. The liver edge was palpated at the level of the umbilicus. There was marked peripheral pitting edema.

Verodigen was given in dosage of 1/80 grain every four hours for five doses followed by 1/240 grain every night. At the end of seven days, the patient was less short of breath, the apical rate was 70 and regular. There was still present some moisture in the lung bases and peripheral edema. Two months later, the patient appeared definitely improved except for continuance of the edema, apical rate 70. No arrhythmia. The patient was not seen afterward but communication with his relatives revealed that he had died of some type of lung infection five months after his first visit.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement, myocardial fibrosis
- C Regular sinus rhythm
- D Class II b

G J, a colored male, aged 47, entered the out-patient department on April 23, 1935 complaining of a sudden attack of shortness of breath that started 24 hours before admission.

Physical examination revealed a very dyspneic colored male, with moderate distention of his neck veins. The chest was full of coarse, bubbling, moist râles. The left border of the heart was 2 cm beyond the left nipple line in the fifth intercostal space. The rhythm was regular, rate 90, blood pressure 160 systolic and 100 diastolic. There was no definite liver enlargement or peripheral edema.

Verodigen was given in dosage of 1/80 grain every four hours for six doses followed by 1/240 grain every night. At the end of seven days, the patient was clinically improved. The distention of his neck veins and moisture in his chest had disappeared. The heart rate was 84 and regular. He was followed for five months and at no time had any recurrence of dyspnea.

Cardiovascular diagnosis

- A Unknown
- B Cardiac enlargement
- C Regular sinus rhythm
- D Class II b

W G, a colored male, aged 45, entered the out-patient department on April 25, 1935 complaining of shortness of breath and intermittent swelling of his feet and ankles gradually becoming worse in the past nine months.

Physical examination revealed a dyspneic colored male with moderate distention of his neck veins. There were moist râles in both lung bases. The left border of the heart was in the sixth intercostal space at the anterior axillary line. A diastolic

murmur was heard to the left of the sternum in the third intercostal space The rhythm was regular, rate 90 The blood pressure was 150 systolic and 40 diastolic There was a definite Corrigan pulse and Duroziez murmur over the femoral vessels The liver edge was palpable three fingers below the right costal margin There was moderate peripheral pitting edema

Verodigen was given in dosage of 1/80 grain every four hours for six doses followed by 1/240 grain every night After 14 days, the patient could sleep flat in bed, the pulse rate was 90, moisture in the lungs had lessened, the liver edge had receded, the edema of the lower extremities was subsiding He developed a trans-perineal abscess in the following month, which ruptured, and while in a weakened state, the patient contracted a lung infection and succumbed in June 1935

Cardiovascular diagnosis

- A Syphilis
- B Cardiac enlargement, aortic insufficiency
- C Regular sinus rhythm
- D Class II a

W C, a colored male, aged 59, entered the out-patient department on April 23, 1935 complaining of shortness of breath and swelling of his feet for the past three weeks

Physical examination revealed an elderly, anemic, orthopneic colored male with distended neck veins and marked generalized arteriosclerosis Moist râles were found in both lung bases The left border of the heart was in the sixth intercostal space at the anterior axillary line The rhythm was regular, rate 110, blood pressure 200 systolic and 120 diastolic There was an apical systolic murmur The liver edge was felt at the level of the umbilicus The lower extremities were markedly edematous

Verodigen was given in dosage of 1/80 grain every four hours for five doses followed by 1/240 grain every night After seven days, the patient was less breathless, the pulse rate was 84, the blood pressure was 160 systolic and 90 diastolic, the liver edge was felt 2 cm below the right costal margin, the peripheral edema had lessened The patient continued clinically improved until May 21, 1935, when he began having paroxysmal attacks of nocturnal dyspnea On July 1, 1935, he developed an attack of acute pulmonary edema and succumbed

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement, myocardial fibrosis
- C Regular sinus rhythm
- D Class II b

R T, a colored female, aged 46, entered the out-patient department on August 20, 1935 complaining of shortness of breath, paroxysms of coughing, and swelling of the ankles for the past four months

Physical examination revealed an anemic, dyspneic colored female with distended neck veins and moisture in the lung bases The left border of the heart was in the sixth intercostal space 3 cm beyond the nipple line The rhythm was regular, rate 120, blood pressure 180 systolic and 120 diastolic The liver edge could be felt 3 cm below the right costal margin There was moderate peripheral edema

Verodigen was given in dosage of 1/80 grain every four hours for eight doses followed by 1/240 grain every night After seven days, the patient felt better, the pulse rate was 98, the neck veins were not distended, the moisture in the lung bases had lessened, the liver edge could not be felt, blood pressure was 140 systolic and 110 diastolic One month later, the patient continued to improve There was no evidence of congestive failure, blood pressure 150 systolic and 100 diastolic, rate 88

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement
- C Regular sinus rhythm
- D Class II b

E B, a white female, aged 30, entered the out-patient department on May 16, 1935 complaining of shortness of breath associated with swelling of the ankles for the past two years

Physical examination revealed a moderately dyspneic, white female. There was no distention of the neck veins. A few moist râles were heard in both lung bases. The left border of the heart was in the fifth intercostal space just beyond the nipple line. The rhythm was totally irregular, apical rate 120, radial rate 100, blood pressure 170 systolic and 110 diastolic. A diastolic rumble was heard over the mitral area ending in an accentuated first sound. The pulmonic second was accentuated. There was moderate peripheral edema.

Verodigen was given in dosage of 1/80 grain every four hours for five doses followed by 1/240 grain every night. After three weeks, breathlessness had lessened, the apical rate was 104, radial rate 100, blood pressure 160 systolic and 110 diastolic, the pulse was still irregular. The patient left the city after her last visit and has not returned to the clinic.

Cardiovascular diagnosis

- A Rheumatic fever
- B Cardiac enlargement, mitral stenosis
- C Auricular fibrillation
- D Class II a

F M, a white male, aged 48, entered the out-patient department on July 26, 1935 complaining of shortness of breath on exertion and swelling of his ankles for the past three weeks.

Physical examination revealed a well developed white male with no distention of his neck veins. A few moist râles were heard in both lung bases. The left border of the heart was in the fifth intercostal space just beyond the nipple line, rhythm was regular, rate 105, blood pressure 210 systolic and 100 diastolic. The liver edge was not palpable. There was moderate peripheral edema.

Verodigen was given in dosage of 1/80 grain every four hours for ten doses followed by 1/240 grain every night. At the end of 14 days, the patient felt better, the pulse rate was 90, there was no evidence of congestive failure. He has continued feeling well and after two months the blood pressure was 190 systolic and 100 diastolic, the pulse rate 80.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement
- C Regular sinus rhythm
- D Class II a

H M, a colored male, aged 40, entered the out-patient department on July 30, 1935 complaining of shortness of breath, cough, and swelling of his ankles for the past three months.

Physical examination revealed a dyspneic colored male with distended neck veins and moisture in the lung bases. The left border of the heart was in the fifth intercostal space 4 cm beyond the nipple line. The rhythm was regular, rate 110, blood pressure 180 systolic and 120 diastolic. The liver edge was palpated 3 cm below the right costal margin. There was moderate peripheral edema. The peripheral vessels were markedly sclerosed.

Verodigen was given in dosage of 1/80 grain every four hours for eight doses followed by 1/240 grain every night. After 14 days, the blood pressure was 170 systolic and 100 diastolic, the pulse rate was 90, all of the congestive failure phenomena were subsiding. One month later, the only evidence of cardiac failure was a few moist râles in the lung bases, pulse rate 90.

Cardiovascular diagnosis

- A Arteriosclerosis, hypertension
- B Cardiac enlargement
- C Regular sinus rhythm
- D Class II b

DISCUSSION

The cases in this series were unselected, except that they all showed organic heart disease with congestive failure, and rapid heart rates. None had received digitalis preparations for at least one month previously. Some of them showed auricular fibrillation, others a normal sinus rhythm. The etiology of the heart lesions was in most cases arteriosclerosis with hypertension, in some, syphilis and rheumatic fever, and in others, unknown. In brief, they represent the routine admissions of "congestive heart failure," cases which would ordinarily be treated with digitalis.

It was obvious quite early in our study that the cat unit established experimentally was not an accurate index of clinical dosage. In other words, the dosage determined by biological methods could not be transferred to patients according to the Eggleston method for digitalization. Over and over again, the maximum therapeutic effects were obtained with a dosage far less than that calculated on a basis of the cat unit being 1/80 gr. As nearly as we could judge from a study of our cases, these effects were obtained with approximately 1/3 to 1/2 the calculated dosage. We do not have an entirely satisfactory explanation for this finding. We had expected by analogy with digitalis, that dosages established by biological assay could be used as the basis for human dosage, but we could not confirm this with Verodigen.

It has been contended that the action of Verodigen persists somewhat longer than that of digitalis, an argument which would explain in part the paucity of the required dosage. Since a number of our cases which were followed for several months continued to take only 1/240 gr. of the drug daily, showing neither toxic effects nor return of congestive failure, such a conclusion seems justified. To be able to maintain digitalization with such a small dose (about 1/30 the amount required for digitalization) strongly suggests that the drug is eliminated less rapidly than digitalis. Certainly this was true in the case of biological assays, as shown by Dr. Haag⁵ in his experimental studies.

We found that the total amount of Verodigen necessary for complete digitalization varied from 6/80 to 10/80 gr. Those patients requiring the larger doses as a general rule weighed more and required a longer period of time for digitalization. These figures approximate those determined by

Stroud et al From such findings, we accepted arbitrarily 1/240 gr as a daily maintenance dose It was impossible for us to accurately "titrate" human beings, with a class of patients who could remain in the hospital but a limited time The problem was rendered more difficult by having as criteria symptoms and signs that do not lend themselves to exact measurement Suffice it to say that those of the group who have been followed over a period of months on such a dosage, showed no evidence of toxic reactions or return of decompensation

As was mentioned before, the cases in this group were similar to those in whom we would ordinarily have used digitalis It seems justifiable to say, as a general statement, that the effects produced by Verodigen are qualitatively similar in every respect to those obtained with digitalis When we analyze the various subjective and objective results in these patients, the truth of such a statement is evident All of our cases were in congestive failure, the result of heart disease All showed both subjective and objective evidence of cardiac decompensation Subjective improvement was shown by the disappearance of dyspnea, orthopnea and other distressing symptoms which ordinarily accompany congestive failure An analysis of the objective measurements revealed the same improvement, specifically, a slowing of heart rate, together with a decrease in pulse deficit in those patients having auricular fibrillation, an increase in vital lung capacity, disappearance of râles, ascites and edema, diminution in the size in the liver, and finally, an increased output of urine It may well be argued that some of these results would have been obtained simply by rest in bed It must be remembered, however, that the majority of these patients had been confined to bed at home without improvement, and further, that drugs of the digitalis group have been shown to be necessary in such cases

When we come to compare the effects of the drug quantitatively with those of digitalis, there are certain apparent differences It has been stated by some clinicians that Verodigen produces a therapeutic digitalis action more rapidly than other digitalis preparations It is true that some of our cases showed excellent therapeutic effects as early as the second or third day, but others required a longer time for complete digitalization It does seem probable that Verodigen is rapidly and completely absorbed, when we consider the small dose actually required as compared with the dose calculated from biological assay

Regarding the toxic effects of Verodigen, we have had little experience, for seldom was it necessary to force the drug to such a point However, we have gained the impression that it is very well borne by the gastrointestinal tract, for it produced no gastric symptoms even in those cases where it was given in overdosages For example, two of our cases developed extrasystoles after taking large doses of the drug, but showed no loss of appetite or nausea Another patient, who is not included in this group because his condition was found on further study to be primarily

nephritic, received 1/4 gr Verodigen before developing nausea, even though he did not vomit and continued to have a good appetite. About the time that nausea appeared, he developed a partial heart block. We had given him this large amount of the drug because he was one of the first cases we studied, and we expected that such an amount would be necessary for digitalization. Another patient, a woman weighing 130 lbs, whom we studied early in our series and who was proved later to have malignant nephrosclerosis, received 1/4 gr over a period of 12 days, only becoming nauseated toward the end, but not vomiting. About the time that nausea appeared, she developed a coupled rhythm. We mention these two cases to support the contention that large amounts of Verodigen may be taken without producing severe gastrointestinal symptoms. It will be noted from a study of our case records that two of our patients did show vomiting. This was early in the course of administration, however, and ceased even though the drug was continued in the same dosages.

Practically all of these cases had seven-foot roentgenograms made of the chest on admission to the hospital. This was repeated in about half of the cases after we felt that full digitalization had been secured. Invariably the transverse diameter of the heart showed a decrease of 1 to 4 cm in relation to the diameter of the chest wall.

Electrocardiograms were made on all cases on admission to the hospital, and several times thereafter. We were unable to demonstrate any constant change in the T-wave or S-T interval following Verodigen, except in one case (mentioned above, but not reported in this series) who received 1/4 gr of the drug over a period of 12 days, toward the end of which time he showed a prolongation of the P-R interval, depression of the T-wave, and finally a partial block. We were not surprised at the absence of electrocardiographic changes, for they have been observed infrequently in our experience during the routine use of digitals.

CONCLUSIONS

From our clinical studies it appears that Verodigen exerts the same qualitative therapeutic effects as digitalis, and provokes the same symptoms when given in overdoses.

Our observations are in conformity with previous reports^{4,6} which definitely indicate that the "biological unit" of digitalis is not always an accurate criterion of clinical dosage. The absorption, potency, and rate of elimination are of equal importance.

In the case of Verodigen the relation of "therapeutic unit" to "biological unit" would seem to indicate a persistence of action which is necessary for a prolonged and uniform digitalis effect.

From our studies so far, we have gained the impression that it is very well tolerated by the gastrointestinal tract, and does not produce gastric disturbances even when administered in moderate overdosage.

Following the oral administration of Verodigen excellent therapeutic effects were noted in many cases as early as the second or third day, although others required a longer time for digitalization

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A COMPARISON OF THE SYMPTOMS, PHYSICAL AND LABORATORY FINDINGS OF MYXEDEMA AND PERNICIOUS ANEMIA, WITH A REPORT OF THREE CASES¹

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THE clinical manifestations of myxedema and pernicious anemia are sufficiently alike to account for the fact that the former disease is frequently mistaken for the latter. The similarities and differences of the two diseases, however, have not been emphasized. The purpose of this report is (1) to compare the clinical manifestations of the two diseases, (2) to present two cases of myxedema in which it was difficult to exclude pernicious anemia, and (3) to report another case of pernicious anemia and myxedema. The data were obtained from the records of 100 unselected cases of pernicious anemia and 33 cases of myxedema.

Symptomatology Both diseases are chronic as a rule, with varying degrees of debility. In fact, the debility may be the only presenting symptom. The occurrence of the usual symptoms referable to the hematopoietic, circulatory, gastro-enteric, and nervous systems in the two diseases is listed in table 1.

TABLE I

Occurrence of symptoms referable to hematopoietic, circulatory, gastro-enteric and nervous systems in pernicious anemia and myxedema

	Pernicious Anemia			Myxedema		
	Pos	Neg	Not Stated	Pos	Neg	Not Stated
Pallor or anemia	81	8	11	18	6	9
Sore tongue or rectum	57	19	24	3	11	19
Jaundice	59	34	7	5	3	25
Constipation	62	34	4	22	6	5
Alternating diarrhea and constipation	19	70	11	3	27	3
Dyspnea	65	17	18	22	8	3
Edema	33	59	8	25	5	3
Paresthesia	80	12	8	13	5	15
Awkwardness	15	1	84	9	2	22
Ataxia	45	4	51	18	2	13
Mental changes	18	1	81	18	1	14
Slowed up	1	0	99	16	0	17
Cold sensitivity	6	1	93	27	2	4

Since the histories were obtained by different physicians in the routine manner, the frequency of occurrence of the symptoms is not comparable. The symptomatology of the two diseases may be indistinguishable. Sore

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tongue and jaundice, which are common in pernicious anemia, may also occur in myxedema, and intolerance to cold and slowness of muscular and mental activity which are common in the latter disease may be present in the former. Paresthesia, which is considered to be one of the cardinal symptoms of pernicious anemia because of its frequency, occurred in more than one-third of the cases of myxedema.

Physical Findings The general appearance of the patients may be similar. Pallor is prominent in both diseases. Myxedematous deposits do not occur in pernicious anemia but they may be slight and easily overlooked in patients with myxedema. The brownish pigmentation of the skin in myxedema may suggest an icteric tint but the sclerae are clear. While five of the patients gave a history of jaundice, it was not present at the time of examination. The atrophic tongue found in pernicious anemia was observed in three cases of myxedema.

TABLE II

Occurrence of neurological findings in pernicious anemia and myxedema

	Pernicious Anemia			Myxedema		
	Normal	Diminished	Not Stated	Normal	Diminished	Not Stated
Reflexes	69	27	4	2	22	9
* A M R	19	6	75	3	17	13
Pallanesthesia	18	76	6	13	8	12
Two point discrimination	25	40	35	10	3	20
Pain	56	6	38	14	2	17
Thermal	44	6	50	12	2	19
Cotton	51	6	43	12	2	19
Position	60	16	24	12	2	19
Ataxia	absent 5	present 14	81	absent 7	present 9	17
Paralysis	absent 5	present 0	95	absent 16	present 1	16

* Alternating motion rate

It is to be noted from table 2 that the neurological changes common to pernicious anemia may also be observed in myxedema. The eight patients with myxedema who showed partial or complete pallanesthesia were less than 50 years of age, therefore the pallanesthesia which is frequently observed in patients over 55 years of age was not a factor. A decrease or loss of the sensations of two-point discrimination and position is rare in myxedema, while it is common in pernicious anemia. On the other hand, a decrease of the alternating motion rate of the tongue or hands is commonly encountered in myxedema but rarely observed in pernicious anemia. Ataxia may be present in both conditions and varies from slight unsteadiness upon turning quickly to complete abasia. An extreme stagger was observed in two patients with myxedema and in two instances abasia was present.

Laboratory Findings The anemia of myxedema usually has a color

index below 1.0 but in 12 of the cases studied there was an anemia with a color index of 1.0 or above. The red blood cells did not show the marked variation in size and shape that is seen in pernicious anemia and true macrocytes are rarely, if ever, present.

Achlorhydria is perhaps one of the most constant laboratory findings in Addisonian anemia, yet it occurred in five of 14 cases of myxedema. The blood bilirubin (van den Bergh) is usually elevated in pernicious anemia and this was observed in 5 of 11 cases of myxedema. The basal metabolism usually is of value in differentiation of the two diseases, in that it is normal or slightly elevated in pernicious anemia and low in myxedema. A low basal metabolic rate, however, may occur in pernicious anemia during and following the reticulocyte crisis. Alt¹ reported one case in which it was minus 28 per cent and Baldrige and Bare² recorded one instance in which the basal metabolic rate fell to minus 20 per cent.

Cases Difficult to Differentiate In spite of the fact that the clinical picture of the two diseases may be similar, the differentiation is usually not difficult. The difficulties that arise occasionally are illustrated in the following cases.

CASE REPORTS

Case 1 A white married female, aged 55, entered the Indianapolis City Hospital complaining of weakness and numbness of the legs. She had always enjoyed good health except for nervousness and vague gastrointestinal symptoms, until four years before the first admission to the hospital at which time weakness and paresthesias were noted. The symptoms decreased two years later following a blood transfusion but the weakness returned, the paresthesia extended to the hips, and vomiting, diarrhea and slight jaundice were also present at the time of the first admission. There was impairment of pressure, thermal, tactile and pain sensations over the legs. The red blood count was 1,880,000, hemoglobin 38 per cent, white blood count 11,900, and the blood smear showed marked anisocytosis and an occasional nucleated erythrocyte. Marked clinical improvement followed two blood transfusions, but during the next seven years, until readmission to the hospital the following symptoms were noted: A gain in body weight, dryness of the skin, loss of hair, absence of sweating, intolerance to cold, swelling of the hands and feet, decreased mental activity, loss of memory, ataxia and a marked staggering gait. The weakness and paresthesia became increased during the last three years of this period and she was referred to the hospital with a diagnosis of pernicious anemia, but upon examination she was found to have myxedema. The reflexes were sluggish and the lower legs were markedly hyperaphic. Pallanesthesia was present to the twelfth dorsal vertebra and the position and thermal senses were decreased over the legs. A marked stagger was present and the Romberg test was positive. The red blood count was 4,270,000, hemoglobin 86 per cent, and the blood smear was normal. Achlorhydria was present, even after histamine. The basal metabolic rate was 33 per cent below normal.

The myxedema subsided following the administration of desiccated thyroid and the neurological condition improved. Five months later the pallanesthesia and Romberg test were unchanged but marked improvement was noted in the gait and paresthesia.

Case 2 A white married female, aged 57, entered the University Hospital complaining of weakness, inability to walk, and pain in the legs. The patient was well until eight years before admission when she noted ataxia, paresthesia, sore tongue

and pallor. The physician consulted at that time made a diagnosis of a "posterior cord lesion." The red blood count was 2,400,000, hemoglobin 50 per cent, and there was no free hydrochloric acid in the gastric juice. The blood Wassermann was 4 plus. She received antisyphilitic treatment with mercury, bismuth and iodides for six months, with some general improvement. Three years later the pallor increased, jaundice developed and the patient suddenly became unable to walk. Within a few minutes she became unconscious and was taken to a hospital where the red blood count was 1,800,000 and hemoglobin 55 per cent. Achlorhydria was again found and prompt improvement followed liver and liver extract therapy. After two months the red blood count was 4,420,000 and hemoglobin 75 per cent, but reticulocyte counts and a basal metabolic rate were not obtained. She continued to improve but the abasia persisted, and dryness of the skin, loss of hair and gain in weight were noted during the three-year period prior to admission. Liver and liver extract were omitted for six months, she gradually became weaker, and was referred to the hospital with the diagnosis of pernicious anemia.

Upon examination she was found to have myxedema and the following neurological findings: A positive Babinski reflex and a decrease of the sensations of position, two-point discrimination and pallesthesia of the lower legs.

The red blood count was 3,140,000 and hemoglobin 75 per cent. Achlorhydria was present even after histamine. The blood bilirubin was normal and the basal metabolic rate was 48 per cent below normal.

The reticulocyte count, red blood count, and hemoglobin did not change following adequate amounts of liver extract before and after the myxedema had been controlled with desiccated thyroid gland. Nine months later the neurological symptoms and findings were unchanged and the red blood count was 4,600,000 and hemoglobin 68 per cent.

Although 20 months later the neurological symptoms and findings were unchanged, she was able to walk with the assistance of a cane. The erythrocyte count was 4.4 million and hemoglobin 82 per cent. The intrinsic factor was found to be absent from gastric juice when analyzed by the method described by Castle³. The negative result in this case may have been due in part to the small amount of gastric juice obtained, which varied from 50 to 150 cc daily. The intrinsic factor, however, was present in comparable amounts of gastric juice obtained from another patient with myxedema who had an achlorhydria without an anemia.

It is difficult to exclude pernicious anemia in the two cases. The normal blood count in the first case is against pernicious anemia, yet spontaneous remissions occur. The failure of the second case to respond to adequate liver therapy before and after the myxedema had been controlled is inconsistent with pernicious anemia, yet there was a primary anemia, a history of definite response following liver and liver extract therapy and the intrinsic factor was absent from the gastric secretions. Cases of co-existing pernicious anemia and myxedema reported by Sturgis and Isaacs⁴ and Means, Lerman and Castle⁵ had a hematopoietic response following liver extract. However, the anemia of myxedema did not respond to liver extract in the cases studied by Baldrige and Greene⁶ and Lerman and Means.⁷

The presence of subacute combined sclerosis in both cases adds to the difficulty, since myxedema is not listed as one of the etiological factors and some neurologists think that it occurs only in pernicious anemia. A review of the neurological conditions that may occur in myxedema by Mussio-Fournier⁸ did not include subacute combined sclerosis. Briggs⁹ observed

two cases of anemia with myxedema and evidence of combined systemic disease, and thought that they were not true pernicious anemia. Both cases were not improved with thyroid therapy and terminated fatally. Lissner and Anderson¹⁰ insinuate that the presence of cord lesions is of grave prognosis in myxedema, but both of my patients responded to thyroid in the usual manner.

Myxedema and pernicious anemia were the only possible etiological factors for the subacute combined sclerosis in my first case, while syphilis was a possibility in the second case. But negative blood and spinal fluid Wassermanns and normal spinal fluid cell count and globulin during the time the patient was in the University Hospital and the absence of other evidence of syphilis, are strong evidence against syphilis as the etiological agent. If subacute combined sclerosis does occur in myxedema, it adds further to the difficulty in differentiation of pernicious anemia and myxedema in some patients.

The following case is reported as an instance of the coincidence of both pernicious anemia and myxedema.

Case 3 A white male, aged 44, entered the University Hospital complaining of weakness, pain in the right chest, and anemia. He had always been well until 1926 when weakness and jaundice were noted. He went to a well known clinic in June 1927, and was told he had pernicious anemia. The red blood count was 1,610,000 and hemoglobin 33 per cent. He was given a liver diet and the red blood count increased to 2,910,000 and the hemoglobin to 60 per cent. A mild subacute combined sclerosis was present at that time. The patient continued to take a liver diet and liver extract intermittently and felt fairly well. During the two or three years before admission to the University Hospital paresthesia became increased and the following symptoms appeared: Slight dyspnea upon exertion, difficulty of hearing, slowness of speech, loss of hair, thickness of the tongue, slow mental reaction, poor memory and sensitiveness to cold. Seven weeks before admission he developed pneumonia which was complicated by pleural effusion. Following this the symptoms were aggravated and he noted awkwardness in buttoning his clothes. The patient was sent to the hospital with the diagnosis of pernicious anemia and pleural effusion, but upon examination he was found to have pleural effusion and myxedema. Paresthesia and absence of the two-point discrimination were found over the lower legs but the position sense was normal. The red blood count was 4,020,000, hemoglobin 58 per cent, and hematocrit 35.5 per cent. The red blood cells in the smear were deeply stained but polychromasia was absent. The size and shape of the cells did not show the variation anticipated for pernicious anemia. A majority of the polymorphonuclear cells contained several lobes. The blood bilirubin (van den Bergh) was normal and free hydrochloric acid was absent from the stomach. The basal metabolic rate was 44 per cent below normal.

With the slight anemia it was felt that the pernicious anemia was not of consequence in the patient's condition and liver extract and desiccated thyroid were given. Prompt improvement in the patient's condition occurred and the red blood count increased to 4,490,000 after one month.

In the cases of coexistent myxedema and pernicious anemia reported by Means, Lerman and Castle⁵ the pernicious anemia antedated the myxedema. This was also true in the case just reported. It must be said that if these

instances of the simultaneous existence of the two conditions are evidence of some relationship between them the nature of this relationship remains entirely obscure

SUMMARY

Although myxedema and pernicious anemia are as a rule easily differentiated, there may be no distinctive features in the history, physical or laboratory findings. The two diseases are not likely to be confused if myxedema is considered in the differential diagnosis of pernicious anemia. The neurological findings, blood smear, and basal metabolic rate are of the greatest value in the difficult cases. Both diseases may be present and a therapeutic test with liver extract may be necessary to ascertain the presence or absence of pernicious anemia, yet a negative response in the presence of subacute combined sclerosis leaves the diagnosis uncertain.

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CONTROL OF THE TOBACCO HABIT¹

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THE physician is frequently called upon to plan a regimen for the patient under his care where it is more or less apparent that some restriction in the use of tobacco is desirable. The indications for such limitation are not clear-cut because the effects of nicotine as a chronic poison to those who habitually smoke to excess are by no means obvious, and are certainly subject to considerable individual variation. Whether nicotine plays a definite part in various forms of vascular disturbance may be open to some discussion, but it is within the practitioner's routine experience to observe that appetite is reduced by smoking, that the sense of general well-being is sometimes adversely affected, that various lesser disturbances (cough, palpitation, nausea, fetor oris, vague indigestion) are at times associated with excessive use of tobacco. Reference to current medical literature shows that the consequences of the abuse of tobacco are being recognized. In the past three years the ill effects of nicotine have been discussed in connection with such varied subjects as peripheral vascular disease, organic and functional diseases of the stomach, pregnancy, headache, hyperglycemia, rhinitis, hypertension, asthma, cirrhosis of the liver, deafness, amblyopia, ether anesthesia, and others. This in face of an endless barrage of propaganda laid down by the tobacco companies in the form of attractive advertising and irresponsible physiology. Some of our "best people" live in a world where one smokes all day long "for digestion's sake," where certain brands of tobacco fail to "get the wind," and are exclusively used by our various champions, where one's private pH is puffed up or down by change in manufacturer—or so at least, according to the back page of almost any magazine. Even our medical journals now carry cigarette advertisements with a scientific flavor. The whole medical directory receives a carton in its mail and any physician who smokes a pack or two is qualified to render a scientist's opinion on the superior merits of the enclosed brand.

It would seem to be accepted that the ill effects of tobacco, whether taken as smoke or otherwise, are largely associated with the nicotine present in the leaf. That a very appreciable amount of this alkaloid is absorbed by the heavy smoker has been demonstrated. The plants from various parts of the world vary widely in their nicotine content, most of our native tobaccos containing a high percentage of the alkaloid. It is also of interest to note that the smoker who does not inhale will absorb only a third less nicotine than the more orthodox smoker, saliva being a solvent for this alkaloid.

If we accept the fact that the use of tobacco in its various preparations is a form of drug addiction, even though a pleasant one not affecting

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criminal statistics, we can more readily help our patient when he finds that his problem has gotten out of hand. Merely to advise that smoking be discontinued is usually futile. The real addict, the smoker of 20 to 50 cigarettes a day, cannot lay aside the habit of years with an easy nonchalance. He has ahead of him wretched days of withdrawal symptoms which will usually end with surrender to the habit which is more deeply rooted than one cares to admit. The moral catastrophe is very like the alcoholic's. Ingenuity is exercised in discovering reasons to escape from the new resolution. In the end, most say in their desperation that no theoretical harm which tobacco might do is enough to make them endure the wretched state of their person, and a return to the old habit very quickly finds them back at the former level of consumption. Marked limitation in tobacco well below a previously established quantity seems more difficult than complete abstinence. In addition to the nervous symptoms which follow withdrawal, the mechanical aspect of smoking or chewing plays some part. After a man has lit a cigar, cigarette or pipe after every meal for many years he will at first be at a loss what to do with his hands at such times. Likewise the confirmed cigarette smoker wants a cigarette between fingers or lips when under any tension.

The first requisite in the cure is a patient who *wants* to stop the use of tobacco in any form. The reasons may be medical, financial, aesthetic, or otherwise, but the determination to discontinue must be there if we are to get any permanent result with the nicotineist—as is true for all addictions.

In an attempt to find some medicinal preparation which would lessen the deprivation symptoms when tobacco is cut off, trial was made of lobelia, which closely resembles nicotine in its effects upon the nervous system.

Lobelia, or Indian Tobacco, the leaves and tops of *L. inflata*, a common wild flower with a blue blossom, was used for smoking and chewing by the American Indians in place of, or mixed with, tobacco. In 1813 Cutler wrote of the use of lobelia in asthma and other spasmodic respiratory conditions. Since then it has been in vaying favor for its local and systemic actions, used chiefly by the Eclectic school. Recently its importance has been as a respiratory stimulant.

Lobelia has been shown to contain five alkaloids, chief of which is lobeline, $C_{22}H_{27}NO_2$. Lobeline exerts almost the same effects as nicotine. There is caused a brief stimulation of the motor centers in the spinal cord and medulla. This stimulation is soon followed by depression, and later paralysis with large doses. The feature of the action of the drug is the stimulation of the motor nerve endings in the involuntary muscles. The symptoms of poisoning resemble those of nicotine: nausea, giddiness, faintness, vomiting, cold sweats. The use of nicotine leads to some tolerance for lobeline.

The usual plan has been to have the patient smoke as is his wont on the first day until the mid-day meal is eaten. All use of tobacco is then

abruptly stopped. The first dose of lobeline sulphate, 0.008 gm (1/8 gr.), is given by mouth in capsule form immediately after the meal. The drug is then further used in the same dosage as the patient may feel the urge to smoke. It has not been found necessary to use over 18 doses in 24 hours and often three or four have been sufficient. The patient decides when a dose is necessary and for how many days he needs this form of substitution therapy. A week of gradually lessening use of lobeline has been ample in most cases, with a few capsules on hand to meet any sudden recrudescence of the former urge. It seems less distressing to start this treatment on a day of rest rather than when the patient is under the pressure of his usual activities.

After the first several doses of lobeline the desire to smoke grows less and less insistent. The hunger returns in waves which are progressively easier to put off without the use of the Indian Tobacco. For a day or two there may be some nausea, a metallic taste, and an uncertain feeling of malaise, but no more unpleasant symptoms have been encountered. As with tobacco, nausea protects against gross over-dosage. The first subjective improvement noted has been a marked increase in the acuity of the olfactory and gustatory senses. One man who had smoked 40 cigarettes daily for at least 15 years said on his third day of lobeline that he was tasting and smelling things which he had almost forgotten. A disconcerting revelation which this latter sense quickly reveals is that the non-smoker suffers in the near presence of the smoker, having lost his protective adaptation. Appetite shows prompt improvement, sometimes to a marked degree, and this can be taken advantage of at once. Nervous, undernourished young women in particular are sometimes seen to undergo a renaissance when tobacco is put away. Likewise, the tense, active, tired man often improves his state of health markedly by interruption of this habit. The irritation of the smoke in the upper air passages is an effect which leaves behind no regrets at its passing. The nasopharynx seems surprisingly clear when freed of this foreign matter. The chronically coated tongue of the heavy smoker loses its covering. Better "wind" is regularly observed. The most gratifying improvement is the increased endurance and the improved sense of well-being which have been reported by former addicts. A definite hypothyroidism developed in two patients about six weeks after tobacco was stopped. It is of interest to consider whether there was any causal relationship here. Another man who had suffered with cold hands and feet for years during the winter, found himself free of this complaint in his first winter without tobacco. Two men use lobeline to restrain their desire to smoke when they must be for some time in places where this practice is prohibited. A "hard night" is distinctly less "hard" when tobacco is omitted. It must, of course, be recognized that excessive use of tobacco may be a result of nervous irritability as well as its cause. Apparently the results have been the same with either sex.

This general plan has been followed out over a period of eight months with a series of patients who had previously tried stopping gradually or abruptly but had all gone back to the pleasant vice. The results have been encouraging. In the great majority of instances it has been stated that there was no comparison between the uneasiness of stopping without lobeline and when this drug is used as a buffer. Once the acute discomforts are passed, the alternate drug is omitted, and then it is a question for the patient to decide whether he thinks it worth while to "stay stopped." He will frequently regret the passing of his former solace but will not again suffer severe pangs for the want of it.

The lobeline can be expected to reduce the misery of deprivation to within relatively easy limits. It is to dull the acute symptoms of withdrawal that the drug is used. After this stage is passed, it is comparatively easy to abstain from tobacco if there is determination to do so.

STUDIES OF THE NITROGEN AND SULPHUR METABOLISM IN A CASE OF CYSTINURIA¹

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SINCE the introduction of satisfactory methods of studying the sulphur partition, a number of cases of cystinuria have been studied without, however, providing a basis for an adequate explanation of the condition. Excellent reviews¹ of the cases so far studied have been published. The metabolic data are confusing and contradictory^{2,3}

Our purpose was to study the effects of diets high and low in sulphur on the cystine excretion in a patient with cystinuria. As will be seen this could be accomplished only indirectly. On account of the intimate connection between the nitrogen and sulphur metabolism, it was desirable to devise a diet or rather a set of diets in which the nitrogen intake would be constant while the sulphur intake varied. Such a diet would also eliminate the influence of the specific dynamic action reported by Lewis⁴. He found that cystine excretion varied with the total protein of the diet rather than with its cystine content.

To this end we used gelatin as the chief source of dietary protein in our test diets. Such a diet contains a minimal amount of cystine sulphur and is low in total sulphur content. From a practical point of view if the cystine output can be reduced, calculus formation should be delayed.

Our patient was a married woman, aged 35, who had had her first attack of renal colic in the winter of 1928-29. It was not until December 1933 that she was operated upon at the Massachusetts General Hospital and four calculi were removed from the left renal pelvis. They were analyzed by Dr Fuller Albright and found to be pure cystine, and we are indebted to him for the opportunity of studying this patient. After removal of the stone, the urinary infection cleared up but cystine crystals continued to be present in her urine. She entered the Peter Bent Brigham Hospital for metabolic study in April 1934. At that time she was symptom-free except for marked hysteria, which is recorded as a usual symptom in a large number of these patients. Indeed this was such a prominent feature that it prevented the blood analysis which we had planned. Usual examinations revealed no deviation from the normal except for the presence of cystine crystals and a positive Millon reaction in the urine suggesting the presence of tyrosine. Her family history presented no evidence of the hereditary factor which has been noted in one-third of the reported cases. We had the opportunity to examine the urines of only two siblings and the patient's son, all of which were negative for cystine. No arthritic tendencies were re-

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pointed out were joint deposits found. This patient, therefore, showed calculus formation and markedly hysterical temperament, but failed to show athritic tendencies or hereditary factors, these four being the usually described clinical features associated with this anomaly. During her stay in the hospital the quantity of cystine crystals varied greatly, as has been the case with all patients observed.

The procedure was that usually employed in metabolic experiments. The diet was calculated from standard tables and duplicate diets prepared, one eaten by the patient, the other analyzed for nitrogen and sulphur. In order to insure constancy, the same foods were eaten every day with particular care to provide the same cuts of meat and parts of vegetables. Table 6 outlines the basic diet and the test diet in which gelatin was substituted as almost the sole source of protein. Urine was analyzed for the various sulphur fractions⁶ and certain nitrogenous elements,⁷ stools for total nitrogen and total sulphur.

In our hands the Looney cystine method⁸ was entirely unreliable, often giving results for cystine sulphur higher than the organic sulphur (cf. table 5). Similar results with this method were obtained by Lewis and Lough and indeed by Looney, Berglund and Graves themselves. Through the kindness of Professor Lewis,⁹ but too late for use throughout this study, we were enabled to use his modification of Lugg's¹⁰ simplification of the highly specific Sullivan reaction. In period 6 of the study (table 5) it was found that the figures of the Looney method and this new method checked very closely indicating that perhaps 50 per cent to 70 per cent of the neutral sulphur in our patient consisted of cystine. During this period (the last) the figures by the Looney method were reasonable in relation to the total organic sulphur, whereas in other periods they were obviously too high. Consequently, our results are based on the figures for neutral sulphur.

TABLE I

Showing the sulphur metabolism during the first experiment. All figures represent 24 hour excretion in milligrams. The percentage of the total sulphur is indicated for the various fractions of the urinary sulphur partition.

Period	Time	Total S	Total SO ₄			Inorganic SO ₄		Ethereal SO ₄		Neutral S		Stool S	S Balance
Number	Days	Mg	Mg	%	Mg	%	Mg	%	Mg	%	Mg	Mg	
I Control	4	634	520	82	473	75	48	7	109	18	92	+ 1	
II Gelatin	4	434	373	86	337	78	36	8	61	14	35	-42	
III Control	4	486	403	83	310	64	99	19	81	17	150	+ 7	

We carried out two experiments on this patient. In the first we substituted gelatin for almost all the protein in her mixed control diet. Recognizing that gelatin is incomplete in other respects than cystine, we added

tyrosine and tryptophane to the gelatin diet in the second experiment. This was especially important in that our patient in all probability had a tyrosinuria also. The feeding of tyrosine in a patient with tyrosinuria and cystinuria might throw some light on the suggested anomaly of the intermediary metabolism said to be concerned in cystinuria.

The first table shows a summary of the details of the sulphur excretion in the first experiment. The so-called organic sulphur fraction of the urine contains the excreted cystine. The normal source of this fraction and its constituents are largely unknown. It behaves much like creatinine in the nitrogen partition and is very constant and unaffected by ordinary fluctuations in food intake. It represents on the average 5 to 10 per cent of the total sulphur excretion at ordinary dietary levels. This patient was on a diet of 58 grams of protein and at this level the organic sulphur should be normally less than 10 per cent of the total urinary sulphur. It may be seen that the organic sulphur fraction was high in all three periods but is diminished both absolutely and relatively when gelatin is the principal source of protein in the diet. Not much change is evident in the other sulphur fractions. There is a noteworthy reduction of the stool sulphur during gelatin feeding. Whether this represents altered digestive processes, as is suggested by the fall in ethereal sulphates, or merely an effort to remain in sulphur balance, is not clear. In table 2 are shown the corresponding details

TABLE II

Showing the nitrogen metabolism corresponding to the sulphur figures recorded in table 1. The period numbers correspond in the two tables. Percentages are of total urinary nitrogen.

Period	Volume	Total N	Urea N		Am Ac N		Creatinine N		Fecal N	N Balance
	c c	gm	gm	%	mg	%	mg	%	gm	gm
I	786	8.0	5.5	69	130	1.6	283	3.5	1.4	- 1
II	1041	9.8	6.3	64	178	1.8	276	2.8	.5	- 9
III	736	7.5	5.7	76	134	1.8	280	3.7	1.5	- 2

of the nitrogen excretion during the first experiment. This patient is in nitrogen equilibrium except during the gelatin period and in this respect behaves normally.^{12 13} The urinary amino acid nitrogen showed a distinct rise in the gelatin period though the concentration is unchanged, owing to a diuresis which in our experience always accompanies the substitution of gelatin as the sole source of protein.

In the second experiment we added tyrosine (1.5) and tryptophane (1.0) to the gelatin diet. In comparing the output during this period with that on the diet containing gelatin alone, it is evident that the addition of these amino acids to the incomplete gelatin reduces both the negative sulphur balance (table 3) and the negative nitrogen balance (table 4). This reduction

TABLE III

Showing the sulphur metabolism during the second experiment All figures represent 24 hour excretion in milligrams The percentage of the total sulphur is indicated for the various fractions of the urinary sulphur partition

Period	Time	Total S	Total SO ₄			Inorganic SO ₄		Ethereal SO ₄		Neutral S		Stool S	S Balance
Number	Days	Mg	Mg	%	Mg	%	Mg	%	Mg	%	Mg	Mg	
IV Control	3	577	452	78	361	63	92	15	125	22	99	+ 3	
V Gelatin plus Amino Acids	5	393	326	83	290	74	36	9	67	17	38	- 14	
VI Control	3	651	456	72	391	60	65	12	195	28	71	- 1	

in negative nitrogen balance cannot be accounted for by the addition of 270 mg of amino acid nitrogen alone At the same time, it will be seen that the amino acid excretion rises higher than in the previous gelatin period indicating that some of the ingested amino acid is excreted unchanged or that the ingestion of amino acids in some other way causes an increase in the amino nitrogen in the urine This period is the only one in which the

TABLE IV

Showing the nitrogen metabolism corresponding to the sulphur figures recorded in table 3 The period numbers correspond in the two tables Percentages are of total urinary nitrogen

Period	Volume	Total N	Urea N		Am Ac N		Creatinine N		Fecal N	N Balance
Number	c c	gm	gm	%	mg	%	mg	%	gm	gm
IV	862	8.7	5.6	64	122	1.4	290	3.3	1.3	- 3
V	851	9.3	6.2	67	250	2.7	280	3.0	1.1	- 5
VI	803	6.8	4.5	66	159	2.3	280	4.1	1.9	+ 5

amino acid excretion is above the usually stated normal Such figures are 1 to 2 per cent ³ of the total nitrogen or a concentration of less than 20 mg per 100 c c ¹³ In table 4 it will be seen that the amino acid excretion exceeds 2 per cent of the total nitrogen in the last two periods, but in the last period the concentration is just below 20 mg per 100 c c However, the excretion in the fifth period is increased over the normal by both the criteria mentioned In period 2, when gelatin alone was fed, the amino acid nitrogen excretion rose from 130 to 178 mg During period 5 the amino nitrogen excretion was 250 mg Thus the addition of 270 mg of amino acid nitrogen to the gelatin diet was followed by an increase of 72 mg in the urinary excretion Since the after period showed a somewhat higher figure than before we may add 25 mg to this figure as total extra amino nitrogen excretion after feeding amino acids This figure is 20 mg less than the

tyrosine nitrogen fed and suggests that some of the tyrosine must have been utilized even if all of the tryptophane was. However, we can say with certainty that about three-fifths of the amino acid nitrogen ingested by this

TABLE V

Showing relation between cystine excretion determined by Looney method and related urinary constituents in the two experiments. It will be seen that this method yielded results that were obviously too high in the first experiment though they closely paralleled the neutral sulphur. The periods are numbered to correspond with the other tables.

Period	Neutral S Mg	Cystine S Mg	$\frac{\text{Cystine S}}{\text{Neutral S}}$ %	Amino Ac N Mg	Cystine N Mg	$\frac{\text{Cystine N}}{\text{Amino N}}$ %
I	109	142	130	130	63	48
II	61	111	182	178	49	28
III	81	125	155	134	56	42
IV	125	102	82	122	48	39
V	67	66	98	250	29	12
VI	195	112	57	159	50	31

patient was deaminized. It is evident, therefore, that this patient with cystinuria and tyrosinuria can utilize only part of ingested amino acids other than cystine. The normal organism excretes all ingested amino acid as urea, and Lichtman¹⁴ has shown that even most patients with hepatic disease can oxidize two grams of tyrosine fed by mouth.

TABLE VI

A tabular view of the diets fed as calculated from standard diet tables. In the other tables the nitrogen and sulphur balance is figured on the results of actual analysis of the food eaten.

	"Normal" gm	"Test" gm
Protein	58	58 (45 gelatin)
Carbohydrate	173	132
Fat	125	118
Calories	2049	1831
Water (including that in food)	1809	1838
Sulphur	0.69	0.14
NaCl	1.57	0.75
Added NaCl	2.00	3.00
Total NaCl	3.57	3.75

In both our experiments this increase in amino acid nitrogen excretion was accompanied by a diminution of cystine nitrogen as estimated from the organic sulphur excretion. However, the increased amino acid excretion might conceivably be due to failure of a deamination in the kidney, as

Krebs¹⁵ has shown that isolated renal tissue possesses powerful deaminizing powers and has postulated that ammonia formation observed by Nash and Benedict¹⁶ is a result of this deamination and is regulated by the neutrality needs of the organism. Unfortunately such studies were not carried out on this patient.

These experiments do not support the idea that cystine output is solely dependent upon the specific dynamic action of protein. These studies may be interpreted as in accord with the hypothesis that this anomaly is concerned with the intermediary metabolism.

In view of the diminution of organic sulphur excretion when gelatin is fed, it seems logical to conclude that the liberal use of gelatin in the diets of these patients might be a useful therapeutic procedure.

SUMMARY

- 1 A case of cystinuria was studied metabolically on high and low sulphur diets using gelatin as a substitute for other protein in the test diet.
- 2 The cystinuric maintains a normal nitrogen and sulphur balance.
- 3 Gelatin feeding decreases the cystine output (as measured by the organic sulphur fraction of the urine) both absolutely and relatively.
- 4 The negative sulphur and nitrogen balance during gelatin feeding is diminished by adding tyrosine and tryptophane to the diet.
- 5 Evidence is supplied by these experiments to support the hypothesis that this anomaly concerns the intermediary metabolism and that in this case other amino acids are abnormally handled.

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THE USE OF HISTIDINE HYDROCHLORIDE (LAROSTIDIN) IN THE TREATMENT OF PEPTIC ULCER^{*}

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DURING the past three years a great deal of interest has been aroused by reports of the use of histidine hydrochloride (Larostidin) in the treatment of peptic ulcer. Due for the most part to favorable immediate results reported, this particular substance has enjoyed a widespread usage. In very few of the reports has there been a sufficient follow-period of observation for really accurate estimation of its true worth in comparison with the time honored dietary and alkaline régime. It has been the hope of the users of this treatment that the long drawn-out medical treatment of peptic ulcers could be avoided and that immediate and lasting improvement would follow. The earliest reports on immediate results were optimistic and tended to bear this out, but subsequent reports and two very recent ones have to a certain extent indicated the fallacy of this hope.

This treatment was introduced by Weiss¹ and Aron² of Strasbourg in 1933. Experimental ulcers were produced in dogs after the method of Mann and Williamson². These ulcers were considered caused by the lack of duodenal juice and its effect on the digestion of proteins. The investigators treated these ulcers by using various combinations of amino acids and produced favorable healing results in a small series of animals. Weiss and Aron⁴ then treated ulcer patients, at first with a combination of histidine and tryptophan, and reported evidence of healing. Later the use of histidine alone was found, by Aron,⁵ to produce the most favorable results.

Since this experimental work many other foreign authors have reported their results in the use of injections of histidine hydrochloride in the treatment of peptic ulcers in humans. Among these are Lenormand,⁶ Bogen-dorfer,⁷ Hessel,⁸ Bulmer,⁹ Stolz and Weiss,¹⁰ and Blum¹¹. Most of these authors report the immediate results in small series of cases and for the most part these results have been uniformly impressive. They have reported not only prompt symptomatic relief, but disappearance of roentgenographic signs and reduction in gastric acidity.

In only one or two instances has a follow-up period been of sufficient length to determine what happens to the excellent immediate results reported. Weiss,¹² in a late report, reports on the treatment of 91 ulcer patients over a period of 18 months.

In this country there have been fewer reports. Volinn and McLaughlin¹³ reported on a series of 21 patients in 1935. In 1936 Volinn

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From the Medical Department, Jefferson Hospital, Philadelphia. The preparation of histidine solution used in this series of treatments is Larostidin supplied by Hoffmann-La Roche, Inc., Nutley, N. J.

and McLaughlin¹⁶ reported on 73 patients, a continuation of their previous preliminary report. They report in both publications 79 per cent of the cases clinically improved after six months with 21 per cent failures. They also report diminution in gastric acidity.

Eads¹⁴ made a preliminary report on the treatment of 35 cases of peptic ulcers with histidine with 65 per cent showing immediate clinical improvement and 35 per cent considered as failures. He found little or no effect on the acid curve. Six of his cases presented roentgenographic evidence of disappearance of the ulcer deformity.

Rafsky¹⁵ reported a series of 26 cases so treated with symptomatic relief obtained in 19 over a four-month period. He observed marked reduction of acid. Practically all of these reports were made on ulcer patients treated as ambulatory cases and with little or no dietary restrictions.

The latest reports on the use of histidine hydrochloride in the treatment of peptic ulcer are those by Sandweiss¹⁷ and Martin¹⁸. These authors treated a series of 40 patients and 41 patients, respectively. They had also a control series of patients treated with diet and alkalis for approximately the same length of time with follow-up periods of one year or more. They, too, found some very favorable immediate results from the use of histidine treatment but after an observation period of from a few months to a year or more found a high percentage of recurrence of symptoms—higher in those patients treated with histidine than in the series treated with diet and alkalis alone.

Sandweiss reports that 85 per cent of patients showing remissions of symptoms due to the histidine treatment returned with ulcer symptoms within six months after treatment. He does not advise the routine use of histidine in the treatment of peptic ulcers but believes it may have a place as an additional weapon in the regular medical treatment armamentarium.

Martin found that his percentage of recurrences was larger than in those cases treated by diet and alkaline therapy. He felt that the results of histidine therapy were symptomatic and transient.

Both Sandweiss and Martin report very little effect on the gastric acidity in their series of cases treated with histidine hydrochloride.

The present report deals with 85 cases of peptic ulcer which have been treated with daily intramuscular injections of a 4 per cent solution of histidine hydrochloride. The number of injections has varied from 15 to 36 with 70 cases receiving 24 injections each.

Each patient was diagnosed definitely a case of peptic ulcer, clinically and by positive roentgenographic findings.

There were 77 cases of duodenal ulcer and 8 cases of gastric ulcer. The average duration of symptoms was six years. The shortest history of symptoms was two months and the longest history indicated 12 years' duration. Fifty-five of these cases had been on previous ulcer treatment, usually consisting of some form of dietary restriction plus alkaline medication.

Eight of these patients had undergone previous surgical operations for their conditions—two having had a perforated ulcer with repair and six having had gastro-enterostomies

In the majority of cases several analyses of the gastric acidity were made before, during and at the completion of the course of treatment

All were examined roentgenologically before institution of the treatment, several during the course of the treatment and all at the completion of the course

Records were kept with regard to symptomatology, weight, et cetera, during the course of treatment

Sixty cases were treated as strictly ambulatory cases with little or no dietary restrictions. Twenty-five cases were treated as hospital cases, but not confined to bed. Ten of these were restricted somewhat as to diet and given occasional doses of alkalis

The patients have been separated into two groups—one group of 45 cases which has been followed for a period of approximately 18 months, the other group of 40 cases which has been followed for a period of six months

IMMEDIATE RESULTS OF HISTIDINE TREATMENT

There were no untoward reactions in any of the cases treated. Temperatures, blood pressures, pulse rates and blood counts were unaffected

There was very little alteration in the gastric acidity. Only eight patients showed any appreciable diminution in acidity and these were those having marked hyperacidity

Eight patients presented roentgen-ray evidence of immediate healing by disappearance of radiological signs of the ulcer. About half of the remainder showed some improvement in the roentgen-ray findings, such as lessened irritability, spasticity and tenderness in the region of the ulcer deformity. The remaining patients exhibited no change in the roentgenologic findings. Gastric ulcer patients presented the best response to the treatment from the roentgenologic point of view

Those patients presenting evidence of obstruction were not benefited by the injections and in two cases were made worse by the treatment

All of the cases previously operated upon showed immediate signs of improvement clinically. Five of these remained clinically improved after one year of observation

A gain in weight accompanied clinical improvement. In some instances this was quite rapid. However, while this gain in weight persisted during the active treatment, it tended to drop off and even be lost during the follow-up observation period in many instances. An increase in appetite and sense of well-being was also experienced in those cases showing immediate improvement

In most cases in which clinical improvement was noted it appeared early in the course of treatment, usually before five injections had been given

In only a few of the cases which showed improvement, was the suggested full number of 24 injections given before relief was obtained. In six cases, 36 injections were given without benefit. In a few cases after 24 injections had been given, there was some improvement noted a few weeks after completion of the course. This suggested some delayed benefit, but it was not permanent. Generally, those cases showing the greatest clinical improvement did so after only a few injections, those having 24 or more injections showed the poorest response.

Gastric ulcers presented the best response clinically as well as from the roentgenologic point of view. Those patients in the younger group with shorter histories and with no complicating factors such as obstruction or hemorrhage also responded more rapidly and more completely to the treatment.

The following tables show results in the two groups of patients, and the percentage of recurrences in those cases showing immediate improvement. These 85 cases have been observed over periods varying from six to 18 months. There are 10 other cases which have been treated but are not included in this series because they failed to return for check-ups and their records are incomplete.

TABLE I
45 Cases 39 Duodenal Ulcers, 6 Gastric Ulcers

Observation time	X-ray healed	X-ray improved	Clinically improved	Unimproved	Recurrence of Symptoms
1 month	6	13	28 (62.2%)	17 (37.7%)	—
6 months	6	11	18 (64.3%)	—	10 (35.7%)
12 months	5	9	14 (50%)	—	14 (50%)
18 months	5	4	9 (35.7%)	—	18 (64.3%)

From table 1 can be seen that of the 28 cases showing immediate evidence of healing 35.7 per cent presented recurrence of symptoms within six months. At the end of 18 months 64.3 per cent show a return of symptoms.

TABLE II
40 Cases 38 Duodenal Ulcers, 2 Gastric Ulcers

Observation time	X-ray healed	X-ray improved	Clinically improved	Unimproved	Recurrence of Symptoms
1 month	2	14	23 (57.5%)	17 (42.5%)	—
6 months	2	6	9 (39.2%)	—	14 (60.8%)

In table 2, 23 cases, or 57.5 per cent showed clinical evidence of healing. Of these, after a six months observation period 14 cases or 60.8 per cent presented a return of their symptoms. This group comprised older patients with longer histories than the group outlined in table 1. There were only

two gastric ulcers in this group both of which presented both roentgen-ray and clinical evidence of healing and remained well. Four of the cases in this group showed evidence of obstruction and did not benefit at all by the treatment.

DISCUSSION

It would seem therefore from the literature on the subject of histidine hydrochloride therapy in the treatment of peptic ulcers that whereas the immediate results secured may be generally favorable, this favorable effect is not continued in a large percentage of cases.

The mechanism by which histidine therapy produces benefit in those cases showing immediate improvement is by no means satisfactorily explained. The theory of Weiss and Aron postulated a deficiency in protein metabolism, with consequent loss of mucosal resistance. It is not accepted by many investigators. Some have held that the stimulation of an increased secretion of mucin might have a bearing, others that there is an analgesic effect produced by the injections. No doubt some of the favorable effects may be due to a psychic effect produced by the injections of a new substance with a considerable reputation. The true mechanism is not yet fully understood.

As other observers have found, the immediate results obtained in the use of histidine hydrochloride are excellent in a large number of cases of uncomplicated peptic ulcer. They compare very favorably with the best results obtained from the rigid dietary, alkaline regimen. However, their end-results after fairly short observation periods are not as good as the end-results following the orthodox medical treatment.

Yet, there seems to be a place for the use of histidine in the treatment of peptic ulcers, for in many cases relief of symptoms is so prompt and so spectacular that this immediate effect alone would justify its use. It would seem logical to employ this new agent as an adjunct to our regular medical treatment.

From the observation of its usage so far reported, histidine hydrochloride therapy cannot supplant the dietary-alkaline medical treatment, but it may be a valuable addition to this treatment, particularly in those cases which do not respond readily to the orthodox measures. In those cases in which further surgery is contraindicated histidine therapy offers aid, such as marginal ulcers and reactivated ulcers following surgical procedure. No attempt has been made to institute a second course of injections after six months in order to determine if there would be any benefit resulting from such a procedure. It might be well to do this.

CONCLUSIONS

Follow-up periods of from six months to 18 months have shown that the favorable results obtained immediately during the active course of treatment

with histidine hydrochloride are not continued in from 35 per cent to 65 per cent of the cases

From the present indications it would appear that the use of histidine alone offers end-results of less lasting benefit than the regular dietary and alkaline therapy in the average peptic ulcer patient. However, combined with the regular orthodox medical treatment, histidine may hasten the good results expected. It certainly is worth trying in those cases resistant to the usual treatment. Further study of the histidine injection treatment should be continued.

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THE RELATIONSHIP OF BACILLARY DYSENTERY TO DISTAL ILEITIS, CHRONIC ULCERATIVE COLITIS AND NON-SPECIFIC INTES-TINAL GRANULOMA

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THE purpose of this communication is to present for critical consideration certain data which have been collected to support the contention that acute bacillary dysentery, acute and chronic distal ileitis, chronic ulcerative colitis and chronic non-specific intestinal granuloma have a common pathogenesis. The evidence to be offered will be considered under the following sub-divisions, viz epidemiological, clinical, serological, bacteriological, pathological and roentgenographical. An effort will then be made to correlate the findings reported under the respective headings and to apply them in diagnosis and therapy. The material which forms the basis for this study includes 400 cases of acute bacillary dysentery (1 major epidemic, 6 minor outbreaks, sporadic cases), 29 cases of acute distal ileitis, 22 cases of chronic distal ileitis, 18 cases of combined chronic ileocolitis and 84 cases of chronic ulcerative colitis. The period covered is from September 1933 to June 1936. These data are supplemented by a 9 to 12 months follow-up study of the Jersey City epidemic which has covered 122 out of an original group of 210 hospitalized patients.

EPIDEMIOLOGY

In the United States the seaport cities are the chief endemic areas for acute bacillary dysentery. The general geographic distribution of acute distal ileitis, chronic distal ileitis and chronic ulcerative colitis corresponds to that of bacillary dysentery. Inquiries show that there are no published or unpublished statistical data now available on these diseases from any source, including the United States Army, United States Public Health Service and the American Public Health Association. The reason is obvious, as ileitis, chronic ulcerative colitis and non-specific granuloma have been regarded as diseases of uncertain etiology. The increasing frequency of observation of these diseases during the last decade is believed to be associated with the increase in bacillary dysentery and not due merely to greater keenness in diagnosis. Outbreaks of dysentery in the New York area occur both in winter and summer often in hospitals through improper isolation of unrecognized cases.

Contact infection in chronic distal ileitis and chronic ulcerative colitis occurs chiefly during the stage of acute bacillary dysentery when the specific

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organisms are present in the feces. The incidence of contact infection in this series of reported cases of chronic disease is 37.4 per cent, a rather high figure since the original source of infection is difficult to determine after one or more years have elapsed. Conjugal infection is relatively common if the couple were married prior to the onset of the original attack of bacillary dysentery or if one partner, involved prior to marriage, still harbors the



FIG. 1. Acute bacillary dysentery (Flexner Y), Stages 1 and 2. Arrow points to hyperplastic lymph nodules (Stage 1). Scattered over the remainder of the mucosa are multiple areas of focal lymphoid necrosis appearing like the mouths of tiny diverticula (Stage 2).

organism. Evidence of conjugal infection occurred in cases 5, 10, 35, 43 (table 1). This does not necessarily signify that both husband and wife will develop chronic ulcerative colitis, or ileitis, but that clinical and laboratory data will often reveal the presence of a previous dysentery infection with the same organism in both.

Because of the importance of epidemiological studies in establishing the pathogenesis of the chronic intestinal lesions a brief summary of some of the

cases will be given. In each instance there was a coincident time factor and the chronic disease represented a definite continuation of the acute phase in a previously healthy individual. Except where otherwise specified the laboratory studies were made in the chronic stage. Titers given refer to the agglutinating power of the patient's serum for dysentery bacilli. In contact cases the titers given are for the same strain of the organism.*

TABLE I
Chronic Ulcerative Colitis—84 Cases

No	Sex	Age	Dura- tion yrs	Agglut	Culture	Phage	Epi- demiology	Surg Path	Necropsy	Roent
1	F	19	1 $\frac{1}{6}$	PH 160			+			+
2	M	45	15	PH MD 320	0	0	+			+
3	F	32	$\frac{1}{2}$	PH MD 160						+
4	F	27	2 $\frac{1}{2}$	PH 320						+
5	F	32	19	MD PH 160		+	+			+
6	F	29	2 $\frac{1}{2}$	MD PH 320	0	0				+
7	M	50	$\frac{3}{4}$	MD PH 320	0					+
8	F	41	1	PH 320		+		+		+
9	M	20	4	MD 160	0	+				+
10	F	35	3	MD 160		+	+			+
11	F	41	1	F 100	+F		+			
12	F	33	4	MD 640	0	0				+
13	M	31	$\frac{1}{2}$	PH 160	0	+				
14	F	35	14	MD 320						+
15	M	40	$\frac{1}{2}$	PH 320			+			
16	M	35	$\frac{2}{3}$	PH 100	0	0	+			
17	M	28	3	PH 160	0	0				+
18	M	47	1	MD PH 160	+MD	+				+
19	M	36	2	PH 100	0					+
20	M	22	11	SD 40						+
21	M		1	MD PH 100			+			+
22	M	22	1	MD 100	0		+			+
23	F	28	1 $\frac{1}{2}$	F 160						
24	F	40	7	PH 640						
25	F	11	$\frac{1}{6}$	MD F 320						
26	F	41	6	MD 40	0					
27	M	42	$\frac{1}{2}$	MD 640	0	0				+
28	M		$\frac{1}{2}$	MD 320						+
29	F	36	2 $\frac{1}{2}$	MD PH 160						+
30	F	27	5		+SD		+			+
31	M	22	2	PH 240	0	+				+
32	M	28	7	PH 320	0					+
33	M	34	6	F 160						+
34	F	35	4	SD 50						+
35	M	37	1 $\frac{1}{2}$	MD 160	0					+
36	M	35	6	MD 640	0		+			+
37	F	38	1	PH 320	0	0	+			+
38	F	47	1	PH 160	0	0				
39	M	38	1	0			+			+
40	M	22	2				+			+
41	M	27	2 $\frac{1}{2}$	MD 640	+MD	+	+			+
42	M	8	2	F 160						+
				MD 320						+

* The writer wishes to gratefully acknowledge the many courtesies extended to him by the physicians and institutions it was his privilege to serve and who furnished much of the antecedent and follow-up clinical data.

TABLE I—Continued

No	Sex	Age	Duration yrs	Agglut	Culture	Phage	Epi- demiology	Surg Path	Necropsy	Roent
43	M	50	1	PH 100		+	+			
44	M	29	1	JC 320			+			+
45	M	53	1	MD 160	0	0			+	+
46	F	35	1	F MD 160						+
47	M	24	1	PH 320	0					
48	F	20	1	MD PH 320	+MD	0				+
49	F	31	1	S 640	+S		+			
50	M	16	$\frac{1}{2}$	PH 80						
51	F	26	$\frac{1}{2}$	MD 320	+MD	0	+			+
52	M	35	6	MD PH 160						
53	M	36	2	PH 160	0	0				
54	M	28	3	PH 100	0	+	+			
55	M	22	1 $\frac{1}{2}$	F 160		+	+		+	+
56	F	35	6	F 320	0		+			
57	M	33	10	PH 640	0					+
58	F	19	$\frac{1}{2}$	MD 320	0					
59	F	57	19	MD 120	0	+	+			
60	M	19	$\frac{1}{2}$	PH 160						
61	M		1				+			+
62	F	35	$\frac{1}{2}$	SD 80	0					+
63	M	13	5	MD 320	0	0	+			+
64	M	30	6	MD 160	0	0				
65	M	14	2	MD 160		+				+
66	M	5	5	MD 160						+
67	M	26	12	MD 320		+	+			+
68	M	22	5	MD PH 160	0	0	+			+
69	F	30	7	PH 320	0					+
70	F	25	1	MD PH 100			+			+
71	F	28	3	PH 40	0	+				
72	M	44	$\frac{1}{2}$	MD 640	0	+	+			
73	F	13	2	MD 160	0	0	+			
74	F	40	1	F 320			+			+
75	M	33	7	PH 320						+
76	M	19	1 $\frac{1}{2}$	PH 100	+PH		+			
77	M	40	2 $\frac{1}{2}$	PH 100			+			+
78	M	35	6	PH 320	0	+	+			
79	F	16	$\frac{3}{4}$	MD 160	0	0				+
80	F	28	$\frac{1}{2}$	MD 320	0	0				+
81	F	20	1	SD 160	0					+
82	F	38	7	PH MD 160	0					+
83	F	22	5	F 240	0	+				+
84	M		1	F 240			+			+

Note In this and the following tables empty spaces indicate no examination made "0" signifies negative, "+" signifies positive F (Flexner Y), MD (Mt Desert), PH (Park-Hiss), SD (Sonne-Duval), S (Schmitz) These strains are all of the mannite-fermenting Flexner type Owing to the heterogeneity of the Flexner antigen several strains were sometimes agglutinated by the same serum Only highest titers are given except where a special point of interest is involved

EPIDEMIOLOGICAL DATA IN CASES OF CHRONIC ULCERATIVE COLITIS (TABLE 1)

Case 2 Male, aged 45 Duration of disease 15 years Started during outbreak of dysentery in U S Army, AEF, during the World's War Titer 1 320

Cases 59 and 5 Mother, aged 57 and daughter, aged 32 Original infection contracted in China 19 years ago Mother's titer 1 120 Daughter's titer 1 160 Bacteriophage present in feces of both Daughter's husband of a recent marriage (three months) now has ulcerative colitis and shows a titer of 1 160 against the

same strain. Two of her children by a previous marriage have had repeated attacks of bloody diarrhea since birth, diagnosed as "colitis." These children are now being treated for colitis abroad.

Case 10 Female, aged 35. Duration three years. Titer 1:160 and bacteriophage present in feces. Husband had acute dysentery at time of onset of wife's symptoms and now has a titer of 1:100.

Case 11 Female, aged 41. Duration one year. Started during outbreak of acute bacillary dysentery in Mexico City. Three others in party definitely diagnosed by attending physician. Titer 1:160. Fecal culture positive.

Cases 15 and 16 Male, aged 40. Duration one-half year. Titer 1:320. Male, aged 35, brother, duration one-half year, titer 1:100. Child of latter has had diarrhea for approximately one-half year, titer 1:100. Two others in family affected but not examined.



FIG 2. Acute bacillary dysentery (Mt. Desert), Stage 3. Discrete and confluent ulceration.

Case 21 Male, age unknown. Duration one year. Follow-up of Jersey City dysentery epidemic.¹

Case 22 Male, aged 22. Duration one year. Titer 1:100. Sister admitted to hospital with appendicular form of acute bacillary dysentery, and at operation there was found acute distal ileitis with mesenteric and mesocolic lymphadenitis. Fecal culture positive and bacteriophage present. Titer 1:100.

Case 35 Male, aged 37. Duration one and one-half years. Titer 1:640. Wife affected during acute stage. Titer 1:160.

Case 38 Female, aged 47. Follow-up of Jersey City epidemic.

Case 39 Male, aged 38. Duration one year. Follow-up of Jersey City epidemic. A son, who was also affected during the epidemic, is free of symptoms.



FIG 3 Case 55, table 1 Chronic ulcerative colitis with polyposis cystica Arrow points to ileocecal valve Accession No 7160



FIG 4 Case 3, table 2 Obstructive granulomatous lesion in distal ileum
Accession No 7938

Case 40 Male, aged 22 Duration two years Titer 1 640 Fecal culture positive and bacteriophage present At onset of disease nursed friend ill with "dysentery" who afterwards died The necropsy findings were chronic distal ileitis and chronic ulcerative colitis with polyposis cystica

Case 43 Male, aged 50 Duration one year Titer 1 100 Bacteriophage present in feces Wife had dysentery at onset of patient's disease Titer 1 160

Case 44 Male, aged 29 Duration one year Follow-up of Jersey City epidemic

Case 49 Female, aged 31 Duration one year Titer 1 320 Dysentery started

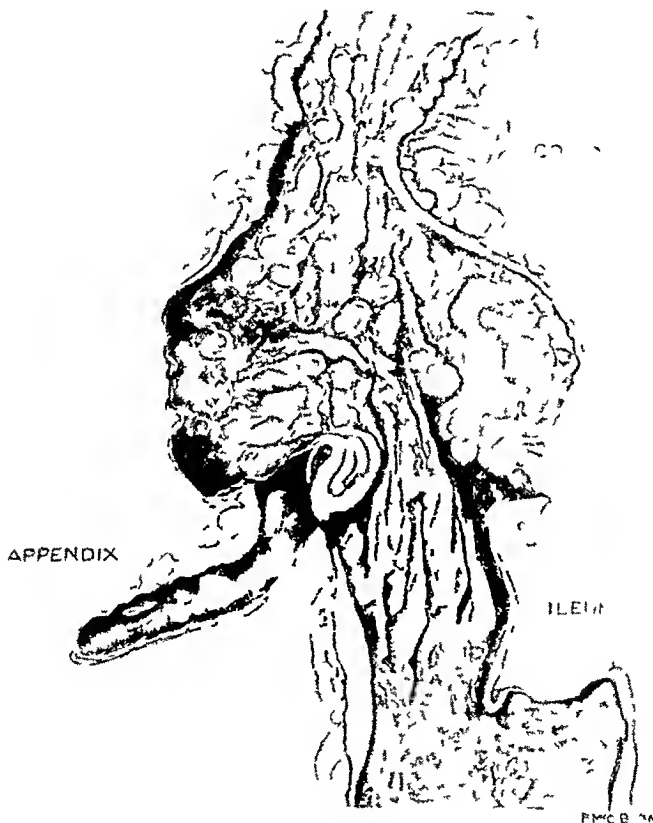


FIG 5 Case 8, table 2 Sketch of ileocecal region Note polypoid areas of intact mucosa, serpiginous and linear ulcerations The process extends into the appendix Accession No 9273

during outbreak in Russia in which a party of visiting scientists, including the patient, were affected Fecal culture positive

Case 51 Female, aged 26 Duration one-half year Titer 1 320 Fecal culture positive Dysentery incurred during outbreak at institution for children where patient worked as practical nurse Her child died of acute bacillary dysentery and necropsy revealed a diffuse acute inflammation of the small and large intestines with follicular hyperplasia and necrosis and an associated mesenteric lymphadenitis

Case 56 Female, aged 35 Duration six years Titer 1 320 Mother, sister and brother have a similar condition but only the sister consented to examination Titer 1 40, subdiagnostic, bacteriophage present in feces



FIG. 6 Case 1, table 3 Sharply segmental and granulomatous type of distal ileitis
Accession No 7500

The possibility of familial contact infection is well illustrated by the following case

Case 67 Male, aged 26 Duration 12 years Titer 1 320 Bacteriophage present in feces Eight others in family affected Upon sigmoidoscopic examination two sisters showed typical lesions of chronic ulcerative colitis One sister had a titer of 1 320 with bacteriophage present in feces Three of her young children have had chronic diarrhea since birth, one having died of it during infancy The other sister had a titer of 1 320 One cousin died of "intestinal hemorrhages" A grandmother and uncle have had "chronic colitis with diarrhea" for many years No further examinations were permitted

Case 68 Male, aged 22 Duration five years Titer 1 160 Two sisters affected with "chronic diarrhea," one having a titer of 1 320, the other 1 160

Case 70 Female, aged 25 Duration one year Follow-up of Jersey City epidemic

Case 74 Female, aged 40 Duration one year Follow-up of Jersey City epidemic

Case 84 Male, age unknown Duration one year Follow-up of Jersey City epidemic

Case 85 Male, age unknown Duration one year Follow-up of Jersey City epidemic

TABLE II
Combined Ileitis and Colitis—18 Cases

No	Sex	Age	Duration yrs	Agglut	Culture	Phage	Epidemiology	Surg Path	Necropsy	Roent
1	M	17	$\frac{1}{3}$	MD 160	0	0				+
2	M	14	$1\frac{1}{2}$	MD 160	0	0	+			+
3	M	35	10	F 160	+F			+		+
4	F	19	4	MD PH 160	0	0				+
5	F	30	1	MD 160	0	0		+		+
6	F	30	2	PH 160	0	0	+			+
7	M	17	3	PH 160	0		+	+		+
8	M	24	5	MD 320	0	0	+		+	
9	F	22	$\frac{1}{2}$	PH 160						+
10	F	23	$\frac{1}{2}$	F 320	0	0				+
11	F	35		MD 320					+	+
12	M	45	1	MD 100	0	0				+
13	F	22	2	F 160	+F		+		+	
14	M		$1\frac{1}{2}$	MD PH 320				+		
15	M	35	2	MD 320	0	0		+		+
16	F	35		MD PH 160				+		+
17	F	15	$\frac{3}{4}$	MD 100	0	+			+	+
18	M	41	$\frac{1}{6}$	F 160		+			+	

EPIDEMIOLOGICAL DATA IN CASES OF COMBINED CHRONIC ILEOCOLITIS (TABLE 2)

Case 2 Male, aged 14 Duration one and one-half years Patient contracted the disease during an outbreak and was seen in the acute stage at which time titer was 1 640 At the end of six months the titer had dropped to 1 160

Case 7 Male, aged 17 Duration three years Titer 1 160 Sister has had chronic ulcerative colitis for same period Titer 1 120

Case 13 Female, aged 22 Duration two years Follow-up of Jersey City epidemic Fecal culture still positive

TABLE III
Chronic Distal Ileitis—22 Cases
(Ulcerative or Granulomatous Type)

No	Sex	Age	Duration yrs	Agglut	Culture	Phage	Epi- demiology	Surg Path	Necropsy	Roent
1	F	26	1½	PH 160				+		+
2	M	34		MD 320				+		+
3	M	25	1½	PH 160	0					+
4	M	45	4	MD 160	0	+				+
5	M	57	14	F 800	0	0		+		
6	F	28	3	MD 160				+		+
7	F	50	5	MD PH 160				+		+
8	M		3	MD PH 160				+		
9	M	30	1	F 160	0	0		+		
10	M		½	MD 160				+		+
11	M	3½	1	SD 100	0					+
12	M	17	2½	PH 100	0	0		+		
13	F	19	½	PH 100	0	0		+		
14	F	20	1	F 100			+	+		+
15	F	21	1	F 120			+	+		+
16	M	31	10	MD 160	0			+		
17	M	32	2	PH 160			+	+		+
18	F	27	5½	PH 640				+		+
19	F	19		MD 640	0			+		+
20	M	35	7	F 100				+		
21	M	16	6	PH F 320			+			+
22	F	32		F 320 PH 160			+	+		

EPIDEMIOLOGICAL DATA IN CASES OF CHRONIC DISTAL ILEITIS (TABLE 3)

Case 14 Female, aged 20 Duration one year Follow-up of Jersey City epidemic

Case 15 Female, aged 21 Duration one year Follow-up of Jersey City epidemic

Case 17 Male, aged 32 Duration two years Titer 1 160 Started during an outbreak of bacillary dysentery following banquet at hotel

Case 22 Male, aged 16 Duration six years Titer 1 320 Sister who nursed him had resection of ileocecal granuloma one year ago Titer 1 320 Her husband has had chronic diarrhea and intestinal symptoms for several years Titer 1 160

There is a possibility that domestic animals may be the source of infection with *B. dysenteriae* in some cases. The only evidence pointing in this direction is that in three instances in this series diarrhea in a dog or cat definitely preceded the disease in the human by six to 24 hours, a common incubation period for acute bacillary dysentery.

CLINICAL

Twenty-nine instances of acute inflammation of the distal ileum were noted as an early manifestation of bacillary dysentery. These cases have been conveniently classified under the appendicular type of bacillary dysentery because of the close clinical resemblance to acute suppurative appendi-

citis^{2,3} There is a short prodromal period of nausea, headache and moderate pyrexia followed by pain and tenderness in the right lower quadrant of the abdomen. The tenderness tends to shift with change in position of the body. There is generally little or no rigidity. The spastic ileum or sigmoid may be felt. At operation, the ileum is found to be reddened, edematous and thickened, the area involved being rather sharply demarcated from contiguous healthy bowel. The vascular arborizations show intense congestion and there is a diffuse acute mesenteric and mesocolic lymphadenitis. There may be signs of an acute upper respiratory infection, particularly in the Sonne-Duval type of dysentery in children. We have not seen acute distal ileitis with mesenteric lymphadenitis in any disease other than bacillary dysentery.

The development of chronic distal ileitis from the acute form of the disease in the same individual has been seen in 14 instances (Table 2, cases 1, 2, 5, 9, 10, 11, 12, 13, table 3, cases 10, 11, 12, 13, 14, 15). The development of chronic ulcerative colitis following an attack of acute bacillary dysentery in the same individual has been seen in 25 instances (Table 1, cases 11, 18, 21, 22, 29, 33, 38, 39, 40, 41, 43, 44, 45, 46, 51, 56, 58, 61, 62, 70, 72, 77, 81, 84, 85). There is not always a clear line of demarcation between the ileitis and colitis group since bacillary dysentery affects both the small and large bowel simultaneously. Usually, the ileum or colon alone is affected in the chronic form of the disease, but the ileocecal valve does not necessarily limit the extent of the lesion. Although the transition stages from acute bacillary dysentery to chronic ileitis or ulcerative colitis were first noted in sporadic cases, perhaps the best illustration is offered in the follow-up studies of the Jersey City epidemic⁴. Of an original group of 210 hospitalized patients 122 were re-studied nine to 12 months later. Forty-six of these patients (37.7 per cent) had persistent or recurring intestinal symptoms or signs, viz. eight (6.5 per cent) had diarrhea with blood, mucus and pus, 12 (9.8 per cent) had a watery diarrhea without gross blood, three (2.4 per cent) had bloody evacuations without diarrhea and 23 (19 per cent) had miscellaneous intestinal disturbances such as recurring attacks of abdominal cramps. In the above group of 46 patients roentgenographic evidence of chronic ulcerative colitis was obtained in eight, sigmoidoscopic proof in two, specimens showing chronic distal ileitis were obtained at operation in two cases and necropsy in one. Thus visible evidence of chronic distal ileitis or ulcerative colitis was obtained in 13 (10.7 per cent) of a total of 122 patients nine to 12 months after the initial attack of bacillary dysentery or roughly one out of every 10 patients. It is possible that these figures would have been higher if routine roentgenographic examinations had been made in every return study.

Abortive and atypical types of acute bacillary dysentery have been recently encountered^{1,5}. They are frequently unrecognized clinically or incompletely studied in the laboratory. In the asymptomatic form, epidemic type, the fecal cultures are positive and intestinal lesions are seen through

TABLE IV

Follow-up Studies of Jersey City Epidemic of Bacillary Dysentery

Total number of hospitalized cases	210
Total number of follow-up cases	122
(a) Roentgenographic evidence of chronic ulcerative colitis	8 (6.5 per cent)
(b) Additional cases with sigmoidoscopic evidence of chronic ulcerative colitis	2 (1.7 per cent)
(c) Chronic distal ileitis (two at operation, one at necropsy *)	3 (2.5 per cent)
* Almost entire ileum and all of colon involved	
Proof of chronic ulcerative colitis or ileitis nine to 12 months after the onset of acute bacillary dysentery (Flexner)—10.7 per cent (13 out of 122, or approximately 1/10)	

the sigmoidoscope, but the patients have no complaint. The organisms disappear in a week to 10 days and the lesions heal shortly thereafter. These patients are discovered only in the course of epidemiological surveys. In the afebrile type the clinical course is typical except for a normal or almost normal temperature. In the constipated type, a bowel movement may not occur for three or four days. This occurs in individuals who usually have one or two normal bowel movements a day. Sometimes a single watery stool is noted at the onset of the disease. Constipation is a frequent symptom in acute bacillary dysentery immediately following the acute stage (seven to 10 days) and suggests Nature's effort at splinting the bowel to favor healing. The meningitic form suggests an acute meningococcus meningitis, but lumbar puncture reveals a clear fluid, normal cytology, the presence of sugar, no globulin and negative culture. Every patient seen thus far has had an associated labial or nasal herpes. Diarrhea usually ensues shortly after the onset of meningitic symptoms. The appendicular form has already been described under acute distal ileitis. Three cases of the agranulocytoid type have been seen, the blood picture bearing a very close resemblance to that seen in agranulocytosis. This phenomenon will be referred to again in connection with the myelotropic toxin.

In chronic ulcerative colitis and ileitis "mendicant's posture" has been frequently encountered. This term is applied to a peculiar position of the body and a characteristic gait seen in ambulatory patients during the period of acute exacerbation of intestinal symptoms. It disappears completely during the remission stage. The patient is generally quite emaciated and dehydrated from frequent watery evacuations. His pallor, hollowed cheeks and sunken temples form an almost funereal background to an expressionless face, or to a worried look which betokens great physical discomfort. In walking there is exhibited a peculiar shuffling gait, the cervical and dorsal spine being bent forward and held quite rigid. The shoulders are high, the head is bowed and the abdomen somewhat concave. The patient appears to be looking at the ground and only casually glances upward at passersby without moving his head. One hand is held on the mid-section or is placed upon the hip. It seems as though only a distaff would be required to complete a picture of the proverbial beggar. It is apparently a natural position

for these patients who suffer from almost constant cramps or abdominal soreness

SEROLOGY

Diagnostic, agglutination titers against *B dysenteriae* were obtained in 22 cases of chronic distal ileitis, 18 cases of combined ileocolitis and 76 cases of chronic ulcerative colitis, or in 116 (93.5 per cent) out of a total of 124 cases. Of the eight cases in which the titers were not done or found to be at the subdiagnostic level, one (case 29, table 1) had a positive fecal culture, three (cases 38, 39, 61, table 1) were originally seen in the Jersey City epidemic and the remaining four (cases 20, 25, 50, 71, table 1) were negative for all bacteriological or serological evidence of bacillary dysentery. All of the chronic cases included in this study were clear cut examples of the disease diagnosed by the usually accepted criteria noted under "Diagnosis." Supplementary data were furnished by pathological study of operative or necropsy specimens. In the serological examinations 18-hour viable broth cultures, the gross test tube method, four hours incubation at 55° C and refrigeration overnight were used. Control agglutination studies of 300 patients from the same area showed diagnostic titers in only 4.6 per cent for all types except *B dysenteriae* Sonne-Duval.⁶ In the latter no positives were obtained. Titers of 1:100 or over were regarded as diagnostic in all except the Sonne-Duval type in which 1:50 or over was considered positive.* Most of our acute mild Flexner and Sonne-Duval infections gave only transitory titers. Hiss⁷ calls attention to the frequent occurrence of weak agglutination titers in bacillary dysentery. It suggests the possibility that a negative titer in chronic ulcerative colitis or ileitis may be inconclusive. In further support of this contention additional evidence is furnished by follow-up titers nine to 12 months after the Jersey City epidemic in 106 cases. Thirty-two (30 per cent) showed a diagnostic titer and 74 (70 per cent) a subdiagnostic or negative titer. Of 11 patients who developed chronic ulcerative colitis or ileitis, eight (73 per cent) showed a follow-up diagnostic titer (table 1, cases 21, 44, 70, 74, 84, table 2, case 13, table 3, cases 14 and 15), one (9 per cent) showed a negative titer (table 1, case 38), the remaining two (18 per cent) not having been tested (table 1, cases 39 and 61).

In some cases peculiar cross agglutination titers were obtained in the chronic stage. Cases 21 and 70, table 1, in which original titers of 1:120 against the Flexner organism were found during the epidemic, showed only 1:40 against the same organism at the end of one year, but a titer of 1:100 against the Mt. Desert and Park-Hiss strains. These results are probably

* There is a lack of unanimity of opinion with regard to diagnostic titers in bacillary dysentery. A rising agglutination titer in acute bacillary dysentery is diagnostic, but in some cases it may not go beyond 1:100. The low titers (1:50) obtained in Shiga-Kruse or Sonne-Duval infections have been repeatedly shown by other investigators. As in the chronic forms of the disease agglutination titer is to be regarded as only one link in the chain of evidence. It should be used only in conjunction with epidemiological, clinical, pathological, bacteriological and roentgenographical studies.

due to the antigenic heterogeneity of the Flexner group. The Flexner organism is said to contain at least four antigenic components, V-W-X and Z,⁸ which are present in every strain but with one component predominating over all the others. Ordinarily this is sufficient to stamp a given organism as a definite type serologically. In *B. dysenteriae* Flexner Y, however, the antigenic components are more evenly balanced and the serum prepared against it has a more irregular and wider range of agglutination against other members of the Flexner group. Owing to the many variants of the Flexner organism a sufficient number of smooth, agglutinable strains should be used, particularly those prevalent in the area in which the studies are being conducted. The Jersey City, Mt. Desert and Park-Hiss strains are always included in our routine set-up. In actual practice, it appears that it is chiefly the severe cases of acute bacillary dysentery or patients with residual infections who develop the chronic lesions. Follow-up agglutination studies of patients who had acute distal ileitis which healed completely, as shown by clinical and roentgenographic examinations, revealed a marked drop in titer at the end of six to 12 months, sometimes to a sub-diagnostic level.

BACTERIOLOGY

It is generally accepted that positive fecal cultures in acute bacillary dysentery are usually not obtained after the first or second week. Repeated and persistent cultural examinations of the feces or intestinal mucosa in chronic ulcerative colitis and ileitis were positive for *B. dysenteriae* in 10 cases out of 70 cultured (14.2 per cent) viz. table 1, cases 11, 18, 29, 40, 48, 49, 51, 76, table 2, cases 3 and 13. In one instance of chronic distal ileitis the organism was recovered approximately one year after resection of the distal portion of the ileum.

Bacteriophage was found in 20 (39.2 per cent) out of 51 cases examined, viz. table 1, cases 5, 8, 9, 10, 13, 16, 30, 40, 43, 54, 55, 59, 65, 67, 71, 72, 78, 83, table 2, case 17, table 3, case 4. It appeared to be group rather than type specific and, when taken in conjunction with other findings, of definite value in diagnosis. In the examination of 100 normal controls, bacteriophage was present in one fecal specimen.

The more often fecal and sigmoidoscopic cultures are repeated, the higher will be the percentage of positive findings. Fresh mucosal scrapings with a dull curette or crypt aspirations are better for culture than feces. For aspiration a heavy walled capillary tube is used (5 mm outside diameter, 35 cm long). A fusiform dilatation, sufficient to hold three or four drops of fluid, is blown into the tube about 2 cm from the distal end which is bent slightly for better approximation to the bowel wall. This inexpensive device, prepared in the laboratory, is inserted through a 12 inch sigmoidoscope, the mucosal aspiration is made by sight and the material seeded directly on a fresh Endo plate. A small one and one-half inch rubber bulb without a valve, but with a hole at the bulbous end is used for

aspiration The bulb is squeezed and the index finger then placed over the hole before suction is started This affords excellent control with a minimal amount of positive pressure in the capillary tube The dilated portion holds sufficient fluid for culture, warm stage and wet smear on hematoxylin examinations for *Endameba histolytica*

Positive culture of *B. dysenteriae* in chronic ulcerative colitis and ileitis is neither an incidental and irrelevant finding, nor is it indicative of a healthy carrier Our experience has been that these patients have never fully recovered from the original attack of bacillary dysentery and that careful physical, roentgenographic and sigmoidoscopic examinations always reveal intestinal lesions Control studies in more than 300 cases failed to reveal *B. dysenteriae* in the feces of individuals free of all manifestations of the disease Our experience in bacillary dysentery points to the existence of "sick carriers" rather than "healthy carriers" In cases 11, 29, 40 and 49, table 1, there were no intestinal or other physical complaints in remission periods nor was an organic lesion suspected by the referring physicians Yet *B. dysenteriae* was recovered in each instance, sigmoidoscopic evidence of ulceration was present and was corroborated in three cases by roentgenographic examinations In two hospital outbreaks in New York City (Sonne-Duval and Flexner Y) the children were at first regarded as carriers or the cultures considered as merely incidental findings Bloody diarrhea in a child who appeared quite well and who had no particular complaints or pyrexia did not correspond to the orthodox picture of acute bacillary dysentery Necropsy findings and epidemiologic surveys revealed the true nature of the disease It recalls to mind the sudden deaths occasionally seen in Sonne-Duval dysentery

Experimental and clinical studies suggest that the primary intestinal lesions in acute bacillary dysentery are due to a thermostabile endotoxin which is excreted from the blood vessels through the wall of the bowel into the lumen Flexner⁹ called attention to this important mechanism in 1906, stressing toxin excretion rather than the local action of the organism itself as being the cause of the intestinal ulcers Zimsser¹⁰ described typical diarrheal and nervous symptoms following the intravenous injection of large doses of toxin into rabbits We have repeatedly failed to infect rabbits by the oral route, but have readily produced diarrhea and intestinal lesions by the intravenous injection of the living organisms or toxin These organisms have been recovered under proper control conditions from the feces of rabbits 24 to 48 hours after the intravenous injection of 18-hour broth cultures

Re-absorption of toxin from the intestine occurs, producing a vicious cycle in the severe toxic cases The major pathologic changes in acute bacillary dysentery are usually produced within the first 24 to 48 hours There are probably a number of toxins produced by *B. dysenteriae* Besides the enteric toxin and thermostabile neurotropic exotoxin, described by Olitsky and Kligei,¹¹ there also appear to be arthritic and myelotropic toxins

which have an affinity for the joints and bone marrow respectively. The incidence of arthritis in both acute bacillary dysentery and chronic ulcerative colitis is quite high. Our figure for the latter is 15.4 per cent (table 1, cases 2, 3, 6, 8, 10, 12, 13, 14, 17, 24, 26, 27, 30, 49, 54, 66, 67, 82, table 2, case 6. Nineteen cases of a total of 124). The larger joints were more commonly affected, particularly the wrists, knees or ankles. Individual fingers or toes were involved less frequently. The exacerbation and remission of joint symptoms corresponded to the alternating periods of recrudescence and subsidence so characteristic of chronic ulcerative colitis and ileitis. Roentgenograms taken during the acute stage of arthritic symptoms revealed peri-articular inflammation in two cases (table 1, cases 10 and 26). The intradermal injection of 0.1 cc dysentery toxin (approximately 1 MLD white mouse) produced a sudden and marked flare-up of joint pains in many instances. This was particularly noteworthy in case 30, table 1, the patient requiring morphine for relief.

The only evidence suggesting a myelotropic toxin is the frequency of leukopenia and the occurrence of three instances of marked fulminating neutropenia resembling agranulocytosis in acute bacillary dysentery.¹² The toxin appears to affect the endothelium of the bone marrow sinusoids preventing the migration of granulocytes from their extra-vascular zone of formation into the circulating blood. Pathologic study reveals no deficiency in leukopoiesis or erythropoiesis in the marrow.

The secondary intestinal lesions are essentially intramural infections with the enterococcus, and hemolytic and non-hemolytic *B. coli*. These organisms gain entrance through the denuded intestinal mucosa, advance along the lymphatic pathways and are persistent and difficult to eradicate. Sudden, spontaneous remissions in chronic ulcerative colitis seem to be due to an increase in the immunity defense mechanism. Preliminary studies point to an increase in the agglutination and bactericidal titers of the blood during the remission stage. Recurrence of symptoms follows a lowering of this defense mechanism so that chronic ulcerative colitis or ileitis is often a cyclic disease corresponding to alternating periods of relatively high and low degrees of immunity. A knowledge of this natural trend should govern the evaluation of any given form of therapy.

The enterococcus and *B. coli* have been isolated from intramural abscesses and secondary lesions of the renal pelvis. Aspirated fluid from inflamed joints in acute bacillary dysentery, chronic ulcerative colitis and ileitis has proved persistently negative upon culture. Secondary toxin absorption effects may be present due to the presence of toxic anaerobes such as *B. welchii* in the bowel. This factor should be borne in mind in connection with intestinal oxygenation.¹³

PATHOLOGY¹⁴

In order to understand the pathological lesions in chronic ulcerative colitis and ileitis, it must be remembered that any part of the small or large

intestine may be involved during the stage of primary infection with *B dysenteriae*. "Skip" areas of segmental involvement may occur. The small and large intestine may be affected independently or concomitantly. In the former, the distal portion of the ileum is usually involved and in the latter, all or part of the large intestine including the appendix. In every case thus far studied sigmoidoscopic examination revealed acute lesions so that it may be stated that in the acute stage of bacillary dysentery the recto-sigmoid is always involved. Repeated sigmoidoscopic examinations starting within a few hours after the onset of symptoms indicate the earliest lesion to be a hyperplasia of the solitary acuminate lymph nodules which are affected in a multiple and punctate fashion. There is an acute diffuse inflammation of the overlying mucosa which is covered with a mucoid, blood-tinged or purulent exudate. Bleeding occurs after the slightest trauma such as passage of the sigmoidoscope or use of a dull culture cuvette. Follicular necrosis quickly ensues, but "weeping" of blood appears to take place even before superficial ulceration is evident. Studies at this stage were supplemented by necropsies on infants. The solitary acuminate lymph nodules are in various stages of hyperplasia and necrosis, the overlying mucosa being ulcerated and the necrotic lymph nodules appearing like the mouths of tiny diverticula. In the severe cases the entire lymph nodule is eventually destroyed. Adjacent areas of necrosis and ulceration coalesce, thus adding width and depth to existing ulcers. The necrotic mucosa is bordered by a marginal zone of polymorphonuclear leukocytes, some lymphocytes and plasma cells. Necrosis of the submucosal blood vessels underlying the ulcerated area occurs and is probably due to the dysentery toxin. The vessel wall ruptures and releases its contents into and through the ulcer. An intense vascular congestion is present throughout this period. In fatal cases serpiginous and geographic areas of denudation occur, the acute inflammation permeates the entire intestinal wall and death occurs from intense toxemia or perforation or both. This process generally takes about two to four weeks in adults in the Flexner and Sonne-Duval types of dysentery seen in the New York area. In infants, death is usually due to toxemia and dehydration which are apt to prove fatal within a few days to one week.

If one can judge from the follow-up figures of the Jersey City epidemic approximately 90 per cent of the cases of acute bacillary dysentery recover completely. The other 10 per cent recover partially or temporarily only to suffer periodic exacerbations and remissions every few weeks or months. In these cases the acute lesions do not heal. Ulcerations persist and spread and secondary intramural infection occurs. That this process is merely a perpetuation of the acute dysentery is borne out by repeated follow-up examinations which prove that neither have the intestinal ulcers healed nor have the symptoms ever cleared up. The disease has reached the chronic phase and whether the process is confined to the ileum or to the colon, the pathologic process is essentially the same. Mural fibrosis ensues and represents an attempt at healing. The lymph nodules are destroyed. Here and

there islands of mucosa may remain intact and often, due to the blockage of ducts by scar tissue and the accumulated secretion, may take on a polypoid appearance. In the ileum or cecum particularly, a granulomatous lesion may be encountered.¹⁵ It merely represents a productive type of inflammation. The presence of giant cells may suggest tuberculosis, but specific stains and guinea pig inoculations with the macerated tissue always prove negative. In general, the end result is an ulcerated, narrowed, thickened, infected, vascularized tube of connective tissue. This is the late stage of bacillary dysentery, perhaps more generally termed chronic distal ileitis, non-specific granuloma, and chronic ulcerative colitis. The pathological changes above described account for the roentgenographic findings in these diseases, viz Kantor's string sign of chronic distal ileitis,¹⁶ obstructive lesions at or near the ileocecal region (granuloma), irregularities of mucosal pattern (ulceration), loss of haustration, narrowing of the large bowel or polyposis. Fistulous tracts and secondary extramural abscesses occur as complications due to extension of the infection through the wall of the bowel. Fortunately the process is often a comparatively slow one so that when perforation does take place there is a well walled off area of inflammation which prevents a diffuse peritonitis.¹⁷ Residual infections with *B. dysenteriae* may occasionally be found in the mesenteric or mesocolic lymph nodes.

Pathological Reports Following is a brief summary of the relevant surgical pathology or necropsy findings in individual cases.

Chronic Ulcerative Colitis (table 1)

- Case 8 Ulceration, intramural infection with fibrosis of the cecum and ascending colon (Surgical resection)
- Case 45 Ulceration, intramural infection with fibrosis and polyposis cystica of the ascending, transverse and descending colon. Perforation of sigmoid (Necropsy)
- Case 55 Ulceration, intramural infection with focal abscesses, polyposis cystica of entire large bowel. Beginning perforation in sigmoid (Necropsy)

Combined Ileitis and Colitis (table 2)

- Case 3 Obstructing granuloma 10 cm of distal ileum (Surgical resection)
"Skip" type of lesion in colon (Postoperative study)
- Case 5 Ulcerative, non-stenosing type of ileitis involving 10 cm distal ileum
Chronic ulcerative colitis (Laparotomy without resection)
- Case 7 Ulcerative and productive type of distal ileitis involving 12 cm of ileum (partial resection) Chronic ulcerative colitis of the cecum and ascending colon (postoperative study)
- Case 8 Ulceration, mural fibrosis and polyposis of the distal 30 cm of ileum, appendix and entire colon (Necropsy)
- Case 11 Approximately the distal half of ileum and entire colon were the seat of innumerable discrete and confluent ulcers with many areas of low grade local peritonitis. Perforation of sigmoid (Necropsy)
- Case 13 Ulceration, mural fibrosis and polyposis of entire colon, perforation of sigmoid. Early granulomatous lesion distal 10 cm of ileum (Necropsy)
- Case 14 Segmental involvement of ileum approximately 60 cm from ileocecal valve, intramural infection with several sinuses connecting adherent ileum

- and cecum Chronic ulcerative disease with mural fibrosis of ascending colon (Surgical resection)
- Case 15 Chronic ulcerative lesion of distal ileum, with polyposis cystica in proximal colon to splenic flexure "Skip" lesion in upper sigmoid (Surgical resection)
- Case 16 Segmental ulcerative and productive type of ileitis 20 cm above ileocecal valve Similar lesions in appendix, cecum and proximal portion of ascending colon (Surgical resection)
- Case 17 Serpiginous and geographic ulceration with intramural infection from ileocecal valve to anus Many ulcers in healing stage located in distal 40 cm of ileum (Necropsy)
- Case 18 Ulcerative ileocolitis involving almost entire ileum, the appendix and colon Polyposis cystica coli with perforation in transverse colon

Chronic Distal Ileitis (table 3)

- Case 1 Segmental granulomatous type of inflammation involving ileum for a distance of 10 cm at a point approximately 15 cm above ileocecal valve (Surgical resection)
- Case 2 Stenosing, cicatrizing lesion of distal 10 cm of ileum (Surgical resection)
- Case 5 Ulceration with extensive mural fibrosis and stenosis distal 30 cm of ileum (Necropsy)
- Case 6 Ulceration with extensive mural fibrosis and stenosis of distal 35 cm of ileum (Surgical resection)
- Case 7 Thickening and linear ulceration of distal 5 cm of ileum (Surgical resection)
- Case 8 Involvement of several loops of ileum which were adherent to one another, with several sinus tracts between coils of intestine and mesentery Abscess in pelvis (Surgical resection)
- Case 9 Chronic non-obstructive distal ileitis (10 cm) with diffuse mesenteric lymphadenitis (Laparotomy without resection)
- Case 10 Distal 15 cm of ileum involved Extensive intramural infection, fibrosis with stenosis (Surgical resection)
- Case 12 Distal 12 to 15 cm of ileum thickened, inflamed Mesenteric lymphadenitis (Laparotomy without resection)
- Case 13 Distal 10 cm thickened and inflamed No evident stenosis (Laparotomy without resection)
- Case 14 Distal 40 cm of ileum thickened, stenosed and inflamed (Surgical resection)
- Case 15 Distal 20 cm of ileum involved Intramural infection and fibrosis Mesenteric lymphadenitis (Surgical resection)
- Case 16 Distal 30 cm of ileum involved Coils adherent with formation of two fistulous tracts Ileocolic fistula and abscess (Surgical resection)
- Case 17 Involvement of 37 cm of ileum at a point 50 cm above the ileocecal valve Inflamed loops adherent, thickened and covered with plastic exudate Mesentery thickened and adherent Productive, granulomatous type of inflammation with obstruction Adjacent portions of intestine exhibited old ulcers (Surgical resection)
- Case 18 Cicatrizing obstructive lesion distal 15 cm of ileum (Surgical resection)
- Case 19 Granuloma distal 7 cm of ileum causing almost complete obstruction (Surgical resection)
- Case 20 Thickening and inflammation distal 15 cm of ileum Mesenteric lymphadenitis (Resection not done)

Case 22 Granulomatous, obstructive lesion distal 10 cm of ileum (Surgical resection)

ROENTGENOLOGY

Roentgenographic evidence of chronic ulcerative colitis or ileitis was obtained in 84 cases examined. In 60 cases, only the colon was involved, all or in part, in 14 both the distal ileum and colon were involved and in 14 only the ileum was affected. The roentgenographic findings did not always correspond to the surgical pathology or necropsy findings. In the latter, particularly, the lesions found were more extensive than those visualized in the roentgenogram. In some cases the development of the chronic lesions could be traced roentgenographically.

Case 34, Table 1 Onset of the disease in 1932. At this time roentgenographic study of the intestinal tract proved negative. In April 1935, the films revealed chronic ulcerative colitis with polyposis cystica.

Case 66, Table 1 At onset of the disease in 1931 roentgenographic examination was negative. In June 1935, the pictures revealed chronic ulcerative colitis involving the entire large intestine.

Case 79, Table 1 At onset of the disease in 1935 no lesion was noted, but in April 1936, the cecum and ascending colon were involved.

Case 2, Table 2 At onset of the disease in December 1934, there was no evidence of ulcerative colitis. In May 1936, the ileum and entire colon were involved. This patient was observed clinically during both the acute and chronic stages.

DIAGNOSIS

The diagnosis of a typical case of acute bacillary dysentery is usually quite simple. A history of contact infection, a prodromal period of 12 to 48 hours of malaise, headache, anorexia and nausea, accompanied by a moderate elevation of temperature is followed by a profuse, watery diarrhea. The fever increases, cramps and tenesmus are marked and mucus, pus or bright red blood appears in the feces. Sigmoidoscopy reveals an intense acute inflammation with ulceration of the mucosa. The tender, spastic ileum and sigmoid can be felt through a thin abdominal wall. A leukopenia is often present at the onset of the disease and may continue throughout. Different strains of the same organism (e.g. Flexner) behave differently in this regard suggesting the presence or absence of a specific myelotropic toxin. Positive fecal cultures are usually obtained during the first week after which the bacteriophage and agglutination titer increase. The atypical forms of acute bacillary dysentery recently encountered include the afebrile, asymptomatic, constipated, appendicular, meningitic, agranulocytoid and Sonne-Duval. Outbreaks of Sonne-Duval dysentery have been recognized in the United States only in recent years. The child with bloody, diarrheal stools who may not appear to be ill should be isolated at once and studied intensively for *B. dysenteriae*. Contact cases of this type on hospital wards are relatively frequent and the outbreak may die out before delayed studies are completed.

The diagnosis of chronic dysentery is more difficult, particularly if the patient is seen for the first time one or more years after the initial infection. The diagnostic criteria in chronic distal ileitis, non-specific granuloma and chronic ulcerative colitis may be summarized as follows:

- (a) Epidemiologic History of contact infection at the time symptoms *first* appeared
- (b) Clinical Persistent or recurring attacks of abdominal cramps and diarrhea, sigmoidoscopic evidence of ulceration, pseudo-polypoid or mural fibrosis with stenosis, palpation of tender, thickened or spastic ileum or sigmoid, mendicant's posture on standing or walking¹⁸, chronic arthritis, the exacerbations being associated with periodic attacks of diarrhea
- (c) Roentgenographic Defects in the mucosal pattern, loss of haustration, narrowing of the bowel lumen, presence of the string sign, intrinsic obstructive lesion (granuloma)
- (d) Laboratory Culture of *B. dysenteriae* from crypt aspirations or mucosal scrapings, diagnostic bacteriophage in the feces, diagnostic agglutination titer of the blood. The skin test and intestinal smears for cytology may be used as supplementary aids in diagnosis.

Differentiation from amebic dysentery¹⁹ may be made as follows. In acute amebic dysentery the ulcers are discrete, undermined and often surrounded by a hemorrhagic halo. The intervening mucosa is not as acutely inflamed as in bacillary dysentery, but the late lesions of both diseases may be indistinguishable from one another through the sigmoidoscope. In amebic dysentery the ileum is not involved, the trophozoites can be detected in the diarrheal discharge and together with the cysts may often be recovered in the mucosal scraping or biopsy. The therapeutic test with emetine or a suitable substitute is a good one. The same may be said of the oxygen test, for after intestinal oxygenation the amebae appear in great numbers due to their avidity for oxygen. In amebic liver necrosis oxygen has a similar effect, the protozoa emerging quite rapidly from the wall and appearing in the drainage tube. Wet smear fixation in Schaudinn's fluid followed by the iron-haematoxylin stain should supplement all warm stage examinations. Double infections with *B. dysenteriae* and *B. typhosus* or *B. dysenteriae* and *Endameba histolytica* do occur since they generally have a common source. We have had two cases of each. This possibility should be borne in mind when patients are unusually refractory to treatment.

THERAPY

The ideal therapy of chronic distal ileitis, chronic non-specific granuloma and chronic ulcerative colitis is the prevention of bacillary dysentery. The typical and atypical forms must be recognized by the family physician and the patients promptly isolated. Every case of diarrhea, particularly in hos-

pitals and other institutions, should be isolated at once without waiting for the laboratory reports. No harm is done if the bacteriologic findings prove negative and this simple precaution may save the lives of many infants. Basically, it is a public health problem to be solved ultimately with the aid of adequate funds for disease prevention.

There must be stricter supervision of food-handlers, water supply and sewage disposal on land and on board ships. There must be complete freedom from political and business control, both of which foolishly perpetuate the very disease regarding which publicity is shunned. Prophylactic vaccination against *B. dysenteriae* during small outbreaks or epidemics is advisable, as indicated by experimental work on animals. Strains of relatively low toxicity may be used.

In acute bacillary dysentery, a potent dysentery antitoxin must be given within the first 24 to 48 hours to be most effective as the major damage is usually done during that period. It may be supplemented by the liberal use of castor oil in humble imitation of Nature's effort to rid the body of specific toxins and bacteria. Normal saline or 5 per cent glucose in saline should be used freely where indicated by hypodermoclysis or intravenously. Every patient with acute bacillary dysentery should be followed up for one year in order to safeguard him against the chronic lesions. Any patient with acute bacillary dysentery which lasts more than three weeks is a potential case of chronic ulcerative colitis or ileitis and should be treated as such.

In the chronic forms of dysentery active immunization may be effected by the use of D-C vaccine and D-C antiviral (the D-C referring to polyvalent strains of *B. dysenteriae*, *Enterococcus*, hemolytic and non-hemolytic *B. coli*)²⁰. Except during temporary acute exacerbations a high caloric, high vitamin diet should be used. Limitations based upon minimal residues are of doubtful value. It must be remembered that most of the small bowel is still functioning well. Intestinal oxygenation is used to control the anaerobes whose toxins are absorbed through denuded areas, to promote drainage of aerobes from the interstices of the intestinal structures and to quiet excessive intestinal peristalsis. Oxygen also serves as an efficient deodorizer of the foul discharges so commonly encountered. Surgical resection, except as an emergency procedure, is contraindicated as the operator generally cuts through infected bowel wall or overlooks "skip" areas with the result that recurrences are common. Repeated transfusions are valuable, particularly if recovered cases of chronic dysentery are used as donors. Professional donors are now being tested in order to determine specific blood agglutinins against *B. dysenteriae*. Those showing diagnostic titers are used for patients ill with acute or chronic bacillary dysentery, subject to the usual preliminary tests for grouping, cross matching and syphilis. Such transfusions have the advantages of blood from a homologous species in lessening serum reactions and supply both fluid and cells to combat dehydration and hemorrhage. They may be repeated as often as necessary and

preferably given by the direct method. The routine use of emetine to guard against a co-existing amebic dysentery is advisable.

SUMMARY

A correlated study of 553 cases of acute bacillary dysentery, acute and chronic distal ileitis and chronic ulcerative colitis points to their common pathogenesis. The development of the different stages has been seen in individual cases including those seen in a major epidemic. Attention is called to the absence of diagnostic agglutination titers in many recovered cases of acute bacillary dysentery and in some cases of chronic dysentery. Control studies and search for other primary etiologic factors proved negative. Secondary factors influencing the course of the disease or present as the result of it were considered as not falling within the scope of this paper. The close association of acute bacillary dysentery and the group of chronic diseases above mentioned appears to be too constant to be regarded as other than of etiologic significance.

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THE HISTORY OF HOSPITALS, WITH SPECIAL REFERENCE TO SOME OF THE WORLD'S OLDEST INSTITUTIONS

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AMONG the living institutions established by man, few have enjoyed a longer or more honorable history than hospitals. In very early documents, institutions are mentioned which may well be the prototypes of our modern hospitals. Such establishments were known in Ceylon, in India (for animals, as well as man), in Greece (in connection with some of the temples), and even in Ireland. With the exception of some of those in India, none are known to have existed for very long, at least not into the modern times.

As Christianity spread through Europe, a practical manifestation of its charitable teachings was the establishment of various institutions for the care of the pilgrim, the wayfarer, the aged, the ill, and the infirm. In mediæval times, their number increased rapidly, impetus being given to the movement by the Crusades (in the twelfth century), and by the spread of leprosy and the plague (in the twelfth to the fifteenth centuries). Limited though these establishments were, according to our modern standards, some of them attained a remarkably high efficiency for the times. Following the subsidence of the epidemics most of these institutions disappeared, and in general, hospital practice sank to rather low standards for many centuries until it rose to new heights during the past hundred years.

The word "hospital" is derived from the Latin, "hospitium"—a guest, as the institutions were first designed for the reception of wayfarers, pilgrims, and the infirm. Almost all were established by the church, although in England in later mediæval times they were often founded by private benefaction, and in Germany quite frequently as municipal undertakings. Even in these cases, they were usually placed under the direction of a local church or monastery.

The oldest hospitals still in existence are the Hôpitaux in Lyons and Paris, in France. Earliest mention is made of the Hôtel Dieu in Lyons in a manuscript of 580 A D, in which its establishment by Childebert is recorded. This is the oldest hospital which has continued in existence with the same name and the same purpose, its life having now spanned a period of almost fourteen centuries. A number of similar institutions were built in the seventh and eighth centuries at Poitiers, Verdun, Arles, Milan, and elsewhere, but their life was comparatively short. At about this time, leprosy commenced spreading through the European continent, and many institutions were established for the reception of lepers. The term "leprosy" was then a rather inclusive term, including probably a number of different diseases, such as lupus and scrofula, as well as leprosy. The lot of the leper

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in those days was a hard one, outcast from society, bereft of all rights as a citizen, he had no means of making a livelihood. It was natural then to establish places for his care, although these were hardly hospitals, but really places for segregation.

Gradually these institutions tended to develop into different types, certain ones being designated for the care of the sick, the blind, the aged, orphans, lepers, etc. In the course of time the need for some of these became less, and those which are still existent usually belong to one of two general types, first, the almshouse for the care of the aged and indigent, and second, the hospital as defined in the modern sense.

The spread of hospitals was most rapid at the time of the Crusades, when large groups of individuals were moving by various routes to the Holy Land. Great encouragement to the foundation of hospitals was given by Innocent III, to whom is due the establishment of the Order of the Holy Ghost. In about the year 1204, the Pope founded the Ospedale di Santo Spirito at the old Tiber bridge in Rome. Hearing of the efficiency of the Hospital at Montpellier in France conducted by Guy de Montpellier, the Pope sent for him and entrusted him with the directorship of the Order of the Holy Ghost. Under Guy de Montpellier's guidance, the Order administered a tremendous number of hospitals throughout Europe either starting these as new institutions, or taking over the management of hospitals previously established. It has been estimated that almost two thousand were founded in Germany, and probably a greater number in France. A number of these still remain, although the Order gradually declined, being active now only in Italy. Other orders also participated in this movement, especially the Teutonic Order, the Johanniten, and the Order of the Lazarites, the last named devoting itself more particularly to the care of lepers. The brilliant history of the Order of St. John at the time of the Crusades is also noteworthy. The Hospital of St. John in Jerusalem (1099) had a high reputation as an institution of the first rank.

In Islam also, many hospitals were established during the time that the Arabians were spreading their culture through a rapidly extending territory. The Arabians' medical inspiration came largely from the Persian hospital in Djoundisabour (sixth century), at which many of them studied. Returning to their homes they founded institutions which were remarkably well organized for the times. A large number of these hospitals (called "bimaristans") were established at Bagdad, Damascus, Cairo, Aleppo, and elsewhere. There were often separate wards for the specialties (particularly ophthalmology and orthopedics), and provision was made for ambulant patients. A regular staff was in attendance, and the teaching of students was well organized.

In the course of time, there were many changes in fortune and development among the early institutions. The great majority have disappeared. Some have lost their buildings, and persist now only as endowments, or as place names, others have lived through the centuries. Some are very modest

and hardly worthy of their names. Others, proud of their heritage, are among the foremost European institutions. Some of these will be considered in the following paragraphs. The list does not pretend to be complete, it includes more particularly those which are of interest at the present time.

By way of comparison, it may be of interest to note that the western hemisphere has a number of hospitals which date back to early colonial times. The oldest of these is the Hospital of the Immaculate Conception in Mexico City, established in the early 1500's. In Canada, the oldest are the Hotel Dieu du Precieux Sang in Quebec (1639), and the Hotel Dieu de St. Joseph in Montreal (1644). In the United States, the first hospital founded as such was the Pennsylvania Hospital in Philadelphia (1751). There are a number which were established as almshouses or workhouses at an early date, the Philadelphia General Hospital (1751), Bellevue Hospital in New York (1735), the Charity Hospital in New Orleans (1736). These all became hospitals some decades later. In the Philippines, the Hospital de San Juan de Dios was founded in 1596 in Manila.

FRANCE

Although comparatively few of the ancient foundations of France are still in existence, the republic does boast of the two oldest of them all, the Hotel Dieu in Lyons, and the Hotel Dieu in Paris. The former was established by Childebert about the year 542 A.D., and has been conducted as a hospital ever since. Most of the buildings are comparatively modern (1737 to 1842). Surely a history of almost fourteen hundred years devoted to the care of the sick may well furnish an inspiration for us in modern times.

The Hotel Dieu in Paris has almost as ancient a history, which has been well told by Mackay. It was established about 652 A.D., as an institution for the care of the ill among the poor. Very early it showed a tendency to division into departments, being one of the first to establish a separate obstetrical department, a "Service d'accouchement" in the women's annex. In 1300, it is recorded that the hospital had an attending staff of physicians and surgeons. The obstetrical department was conducted by the *sages-femmes*. At this time it had grown to a capacity of eight or nine hundred patients, and probably reached double that size in the fifteenth century. The number of beds was actually much less, as it was the practice to use enormous beds for four to six patients each. Included in the hospital equipment were two bath tubs on wheels.

The Hotel St. Louis in Paris was established by Henry IV in 1607 for plague victims, it now receives cases of diseases of the skin. In 1260, Louis IX founded the Hospital des Quinze Vingts as a home for the blind. Its name indicates a capacity of 300 inmates, and is an interesting survival of the vigesimal system of counting. It is still in operation near the Place de la Bastille, part of its endowment consists of the land on which the Folies-Bergeres is situated.

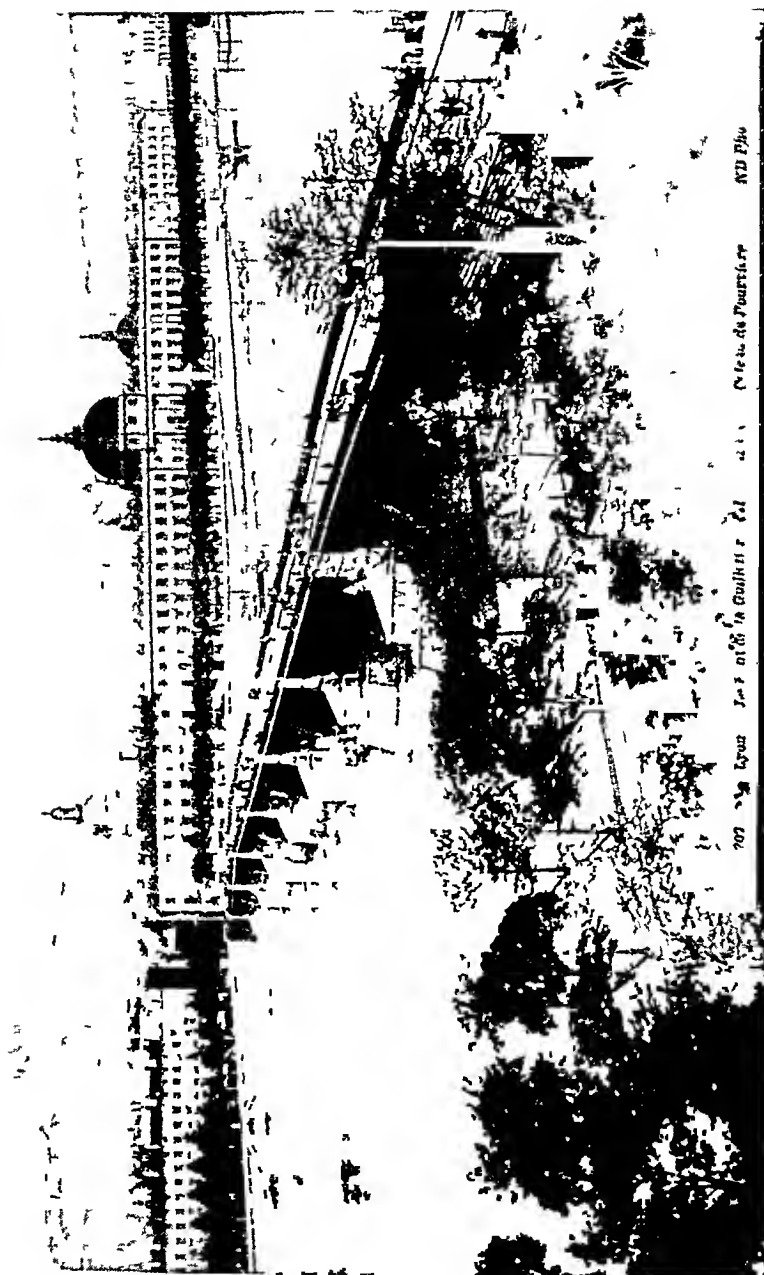


Fig 1 Hotel Dieu, Lyons Founded ca 542 A D Buildings mostly 1737 to 1842
(N D Photo)

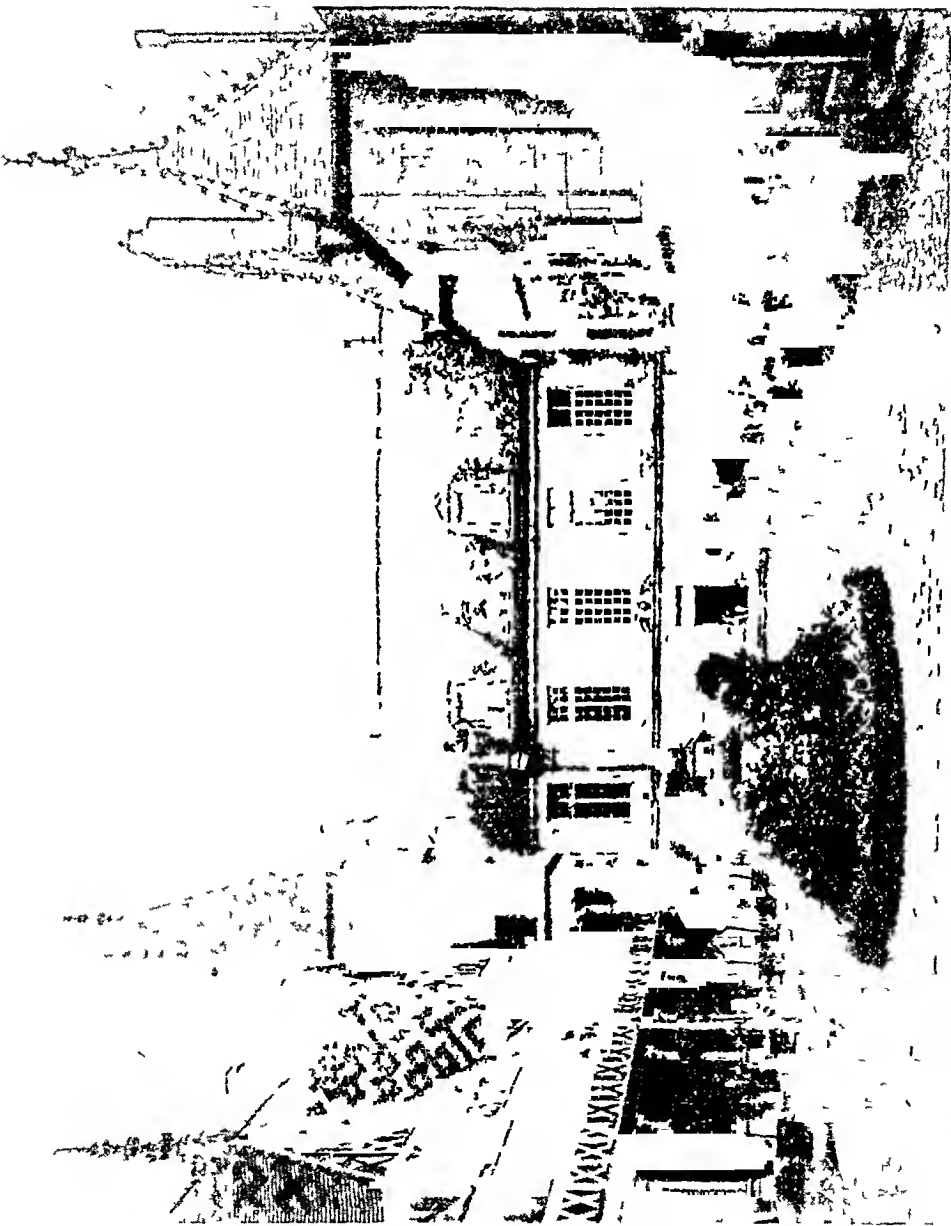


FIG 2 L'Hotel Dieu, Beaune Founded 1443, building occupied 1452 (Arch du T C F)

One of the most charming old hospitals in France is the Hotel Dieu in Beaune. This was founded in the year 1443, and it is the oldest hospital which has continuously occupied its original building. The first patient was admitted January 1, 1452. There are some interesting remains of former hospitals scattered elsewhere through France. Partly in ruins, the "Grande Salle of the Hotel Dieu" at Tonnere is frequently visited on account of its architectural beauty. It was established by Margaret of Burgundy about 1293. In Angers the archaeological museum is housed in the old Hospital St. Jean, which was originally given to the city by an early Count of Anjou, Henry II, King of England (1133 to 1189).

HOLLAND AND BELGIUM

There are several medieval hospitals in Amsterdam and Delft in Holland. In Belgium, the Hospital of St. John in Bruges was established in the twelfth century, though few traces of its early buildings remain. It is still conducted as an active up-to-date institution. In the former chapter room are housed some of Memling's finest work (1430 to 1494). The Hospice de la Poterie in Bruges is an asylum for elderly women, founded in 1276. Damme, formerly the port of Bruges, possesses an old institution, the Hospital of St. John, a home for old persons.

ITALY

As the country in which Christianity first made its rapid spread, Italy boasts a number of early specimens. The oldest is the Santa Maria della Scala in Sienna, established in 898 A.D., with buildings dating largely from the fifteenth and sixteenth centuries. In Rome, the earliest was the Ospedale di Santo Spirito, founded in 1204 by Pope Innocent III, and shortly thereafter turned over by him to Guy de Montpelier as the first of the many conducted by the Order of the Holy Ghost. The buildings date from about fourteen hundred and later. Other old Roman institutions are the Ospedale della Consolazione, with parts dating from the thirteenth century, built on the site of an earlier hospital. The Ospedale di Santa Maria della Scala was established about the fourteenth century. These hospitals are still under the direction of the Order of the Holy Ghost. Other old hospitals in Rome are the Ospedale di San Giacomo, and the Ospedale di Giovanni. In Milan, the Ospedale Maggiore dates from 1456, and now serves as a city hospital. The City of Florence has many early survivals. Santa Maria Nuova was founded in 1287, by Falco Portinari (father of the supposed Beatrice of Dante), the buildings are largely seventeenth century. The Bonifazio (1377) has become an asylum for mental cases. San Giovanni di Dia was founded by Simone Vespucci about 1400.

One of the show places of Florence is the Ospedale de Santa Maria degli Innocenti, which was established as a foundlings hospital, and has served continuously as such up to the present time. The building was commenced

in 1421 after designs by Brunelleschi, and opened in 1444. Its history may be said to start much earlier, as there were combined with it the Hospitals of San Gallo (1218²), and Santa Maria della Scala (1316). For almost five hundred years, this institution has occupied its original building,



FIG 3 Ospedale Degli Innocenti, Florence. Founded 1421, building occupied 1444. The medallions of della Robbia may be seen at the heads of the Columns.

although the interior arrangements have been modernized from time to time. It is a treasure house of early Italian art, possessing many specimens of Ghirlandaio, della Robbia, Brunelleschi, Poccetti, and others. Best known of these are the famous medallions of the infants in swaddling-bands, by della Robbia. There are fourteen of different designs at the head of the columns on the front facade.

The infants were formerly put in a small door opening at one end of the portico, but now most of them are received from an affiliated maternity hospital nearby. Complete supervision is continued until maturity. The institution has always been a favorite charity of the city, though in recent

times the income from its endowment has been augmented by contributions from the municipality. The records of the hospital are practically complete from the date of its foundation, the name of the first infant received is said to have been Agathia.

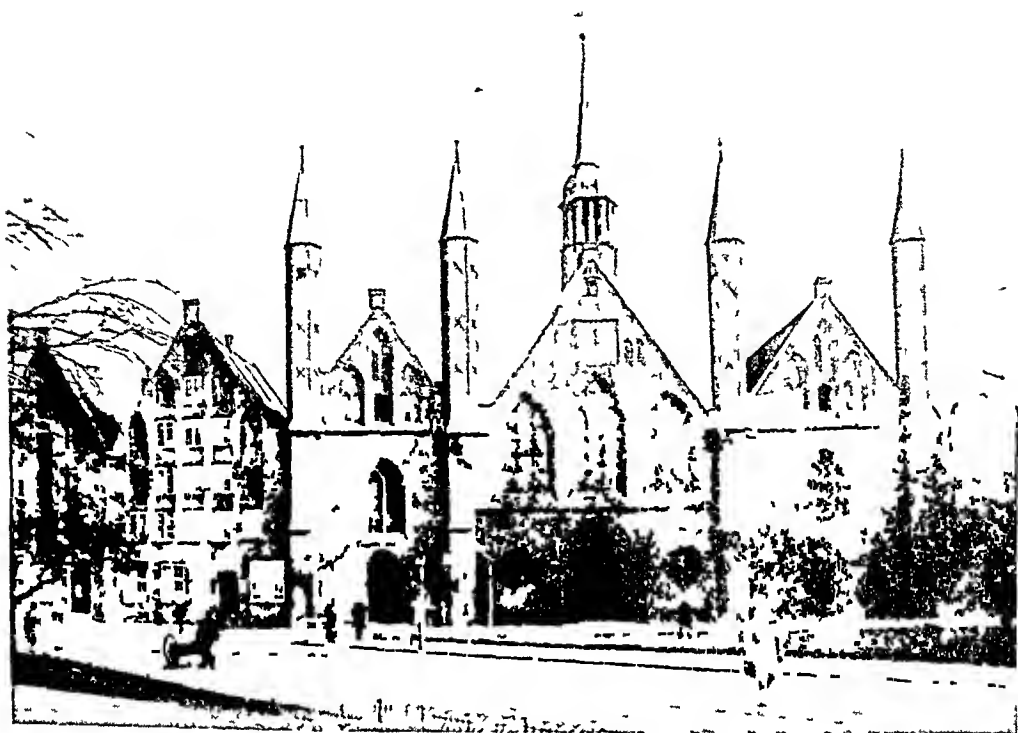


FIG 4 Heiligen Geist Hospital, Luebeck (Ger Tour Info Office, N Y)

GERMANY

Hospital development in Germany took place largely in the thirteenth and fourteenth centuries through the activities of the Order of the Holy Ghost and the Order of the Lazarites. Vinchow differentiates between the hospitals established within the city walls and those established without the city walls. The latter were usually leper houses. He lists a large number of these establishments, some in even the smallest villages in Germany. It is probable that their total number was over 2000 at one time.

The best preserved examples that the writer has seen are the ones at Luebeck and Rothenburg o d Tauber. In the former city, the Hospital of the Holy Ghost has always been an almshouse for elderly people. Originally established in 1240, it has occupied its present site since the 1400's, and retains a part of its early buildings. This institution illustrates one phase in hospital development which was more common in Germany than elsewhere, in that it was established by the municipality. The Hospital of the Holy Ghost in Rothenburg was originally built outside one of the gates, but when the city extended its ramparts it was included within the walls.

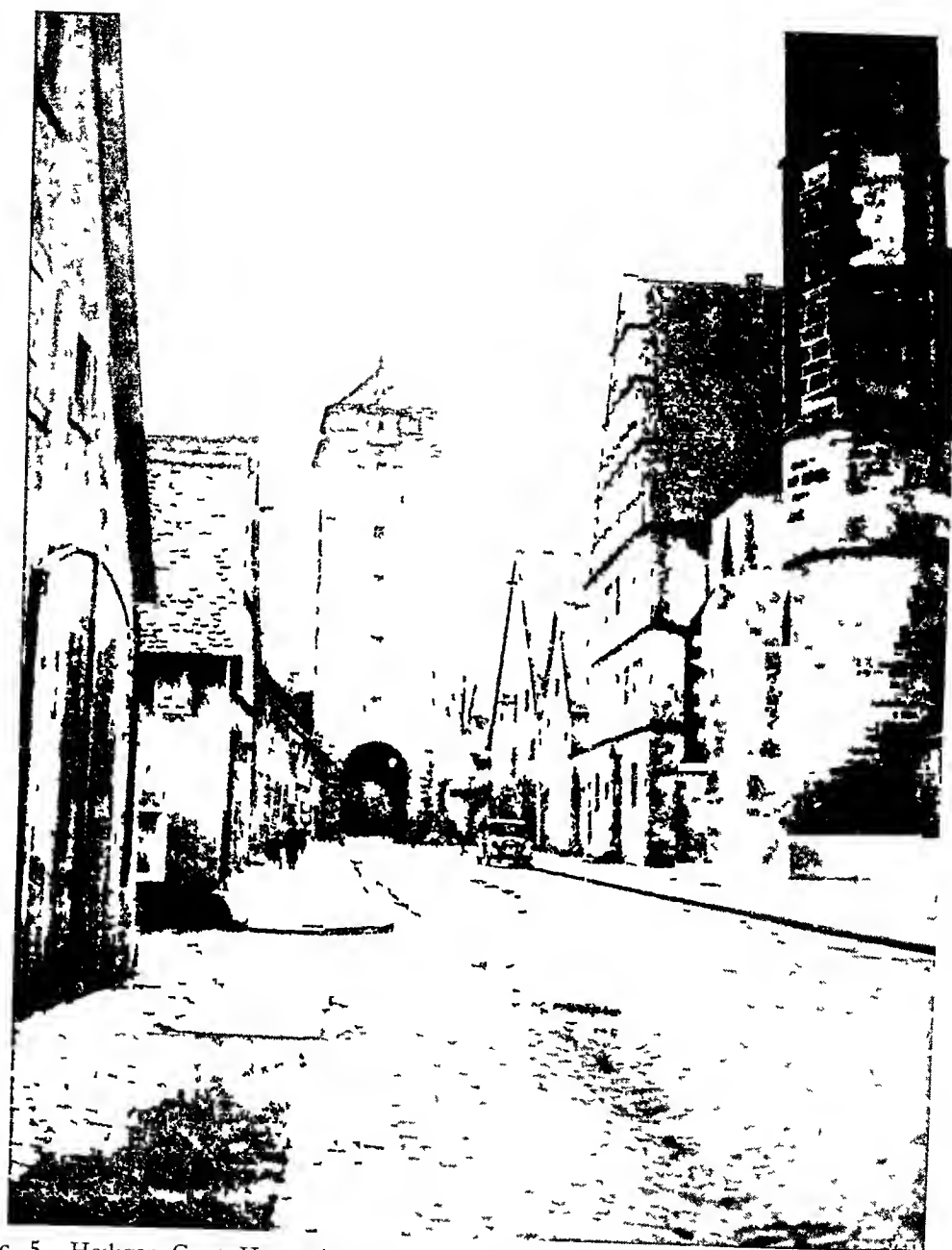


FIG 5 Heiligen Geist Hospital Rothenburg O D Tauber Hospital to the right, city gate in the background

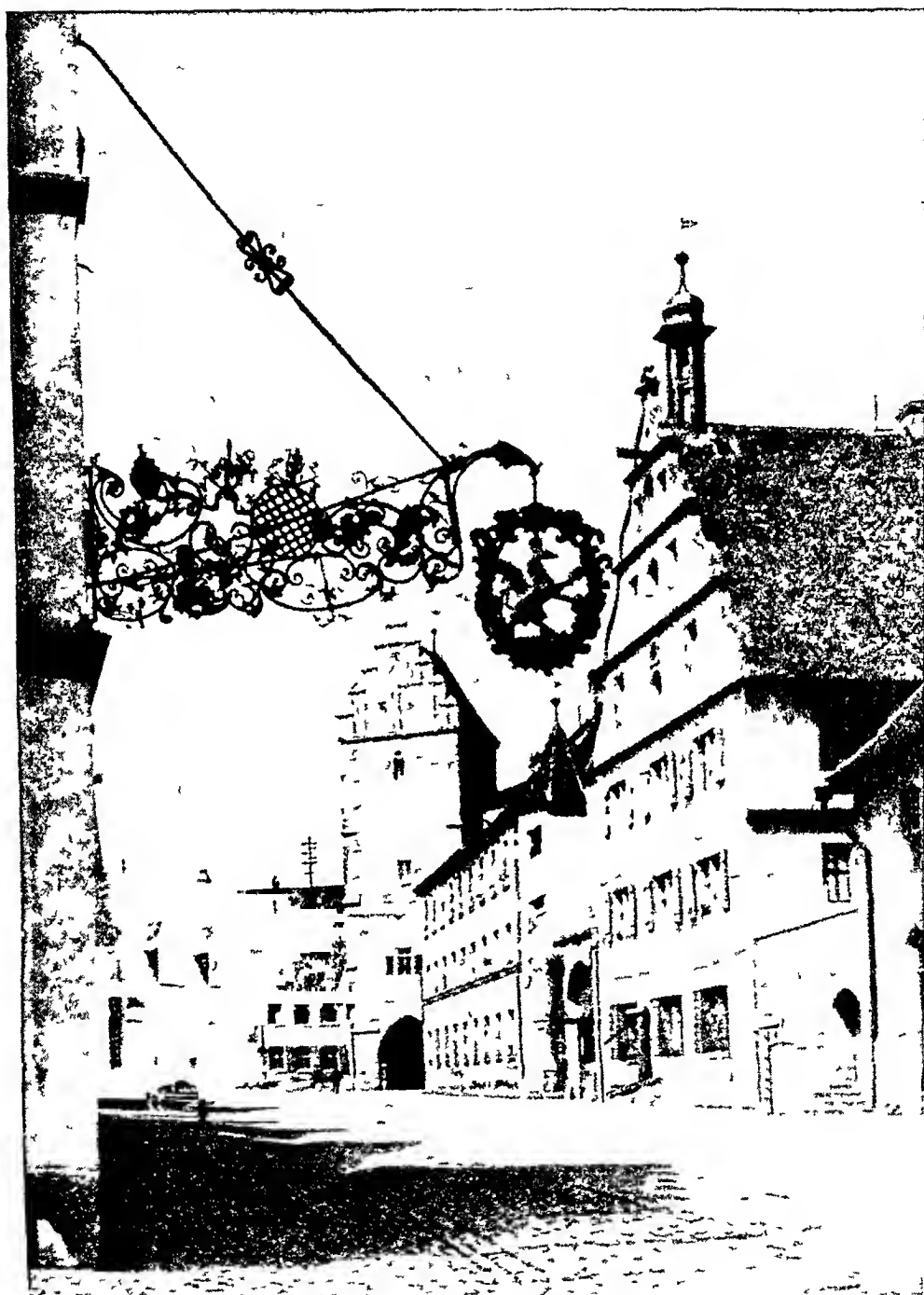


FIG 6 Heiligen Geist Hospital, Dinkelsbuehl Hospital to the right, city gate in the background (Ger Tour Info Office, N Y)

This is an excellent specimen of the small city hospital, the major part of its support now being derived from city funds. The main building dates from the fifteenth century.

Another Holy Ghost Hospital is to be found in the picturesque town of Dinkelsbuehl. It comprises both a home for old people and a hospital, the latter housed in a new building erected in 1864. Additional examples of old hospitals still exist in Nuernberg, Wuerzburg, Luneberg, and in Bremen (St. Georgen Hospital, originally founded as a leper house). In Berlin, a Hospital of the Holy Ghost was built about 1278, but it has entirely disappeared, although there is an endowment remaining which is used for charitable purposes. St. Gertrauden Hospital was founded in the early 1400's "without the walls" on the square called "Spittelmarkt" at the east end of Leipzigerstrasse. It has recently been moved to a new location.

ENGLAND

The first hospital recorded in England was built in York in Saxon times, 937 A.D. After the Conquest, many more were founded. They all suffered severely at the time of the Reformation, though a large number were preserved through the contributions of wealthy citizens. Those that had been founded as lay endowments continued their functions, for such philanthropy was a favorite form of charity by the well-to-do in the fifteenth and sixteenth centuries. Only the institutions in London were hospitals for the sick, those in the small communities were almost invariably of the almshouse type.

Of the hospitals, the most famous is St. Bartholomew's in London, which recently celebrated its 800th anniversary, having been established by Rahere in 1123. This one is well known to many physicians, as it is one of the great centers of medical teaching in the world. Its buildings date from 1760 and later. St. Thomas Hospital comes next in age (1215). St. Mary of Bethlehem was founded for the care of mental cases in 1247 (from its name was derived the word "bedlam").

In numerous towns and villages of provincial England there will be found near the parish church a small building which is the almshouse. These institutions are of varied character as regards the nature of their endowments and the purpose for which they are now conducted. The original endowment usually was in the form of land, and naturally these endowments have been subjected to the vicissitudes of prosperity and depression for many centuries. Sometimes the institution owned the land outright, sometimes it was given a certain allowance from an estate. Certain of these almshouses were founded for the care of a number of old men, or old women, or for couples only. Charming examples are to be found in Canterbury, Sherborne, Burford, Norwich, Chipping Campden, Abington, Exeter, and in innumerable other communities.

Of this group the most perfect architectural specimen is the Hospital of

St Cross at Winchester It was established by Bishop Henry of Blois (a nephew of William the Conqueror) in 1123. It is housed in a double quadrangle of buildings which represent various gifts and additions from Norman times and later. Most of the quarters were built by Cardinal Beaufort in the sixteenth century. It is of the almshouse type providing a home

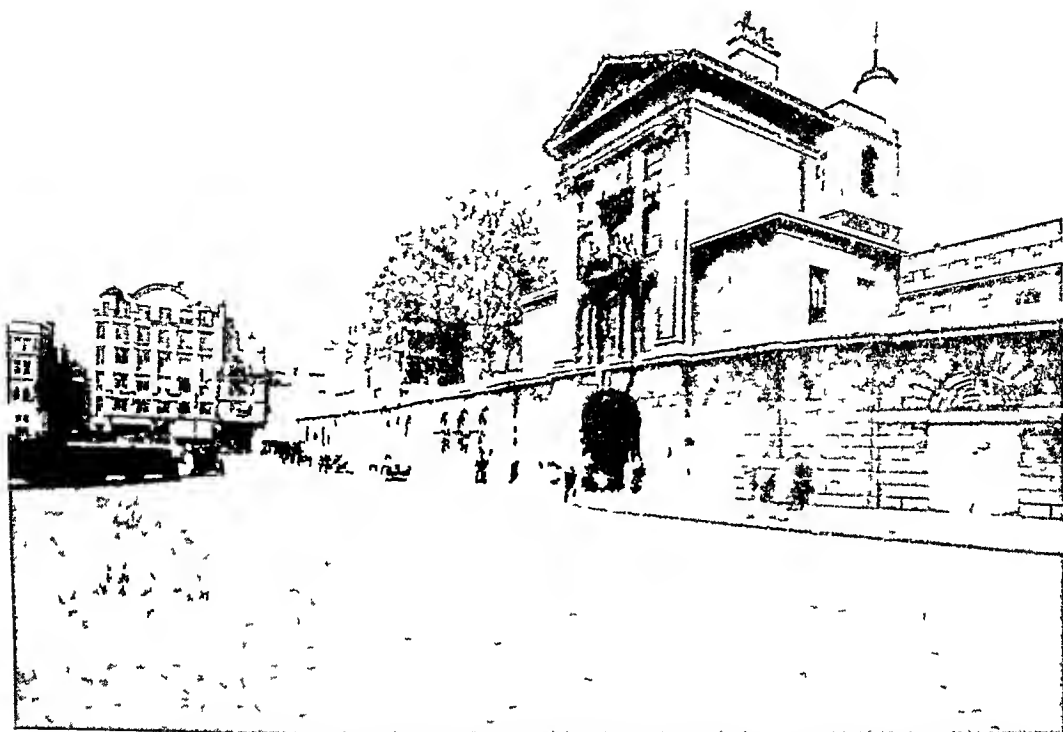


FIG 7 St Bartholomew's Hospital, London. Founded 1123 A.D. Buildings 1760 and later. (Photocrom Co. Ltd.)

for old men, and in addition (as a separate foundation) affords a home for 12 men of "gentle breeding." Its endowment also provides for the "wayfarer's dole," consisting of a pint of beer and some bread, which any wayfarer may have for the asking.

In other countries, there are a number of survivals. Of the many founded by the Arabians, there are several still in existence. The famous Bimaristan El Mansouri in Cairo, commonly called by the name of its founder, Qalaoun (1284), is now devoted exclusively to ophthalmological cases. A new addition to it was constructed about twenty years ago. One of the hospitals in Aleppo dates back to 1344 A.D.

In Spain, the Moors built a number of institutions during the time of their occupation (Cadiz, Seville, Toledo, etc.). The General Hospital in Madrid traces its foundation to three Moorish hospitals which were combined by Phillip II in 1566. There are a number of post-Moorish hospitals

and almshouses dating from the thirteenth to the sixteenth centuries in some of the other cities in Spain

In this brief outline of the history of hospitals it has not been possible to discuss many of the interesting phases in their early development, nor to do more than make brief mention of a few of the hospitals which have been in existence for many centuries. Rich in historical and medical interest, as well as in architectural beauty, many of these institutions are well worth a visit by the physician traveling abroad

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CASE REPORTS

AN UNUSUAL CASE OF OSTEOPSATHYROSIS (FRAGILITAS OSSIIUM, LOBSTEIN'S DISEASE) *

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THE disease which has been called fragilitas ossium, Lobstein's disease,¹ or osteopsathyrosis is characterized by the remarkable symptomatic triad of blue sclerae, brittle bones and deafness. The general features of the disease have been well summarized by Apert,² and by Ottley,³ who give comprehensive reviews of the literature. Ottley lists the following as characterizing the syndrome of osteopsathyrosis:

- 1 Fragility of bone
- 2 Peculiar conformation and structure of bone
- 3 Peculiar shape of the skull
- 4 Laxity of the ligaments
- 5 Blue coloration of the sclerae
- 6 Deafness
- 7 Abnormal electrical reaction of the muscles
- 8 Miscellaneous abnormalities of the teeth, nails and hair and disturbances of the vasomotor system
- 9 Familial character of the disease

Brief comments on these peculiarities may help to delineate the clinical picture more clearly.

1 The bones fracture as the result of injuries so slight that they are often described as "spontaneous fractures." This is not due to a deficiency in calcium content, but is to be ascribed to morphological defects in the architecture of the bones.⁴ The normal calcium-phosphorus ratio of the blood is not disturbed.

2 Changes, seen more distinctly in the long bones, comprise extreme slenderness, incurving of the shaft, most marked in its middle portion, thinning of the cortex and increased transparency to roentgen-rays. The epiphyses show no characteristic change.

3 The occipital prominence of the skull is exaggerated, and there is bulging of the temporal bones. The general effect is as if the entire skull had been subjected to powerful downward pressure on the vertex.

4 The ligaments show a remarkable degree of relaxation. As a consequence pes planus, hyperextensibility of the fingers and knees, and frequent sprains and dislocations are observed.

5 Blue sclerae constitute a very striking feature of the syndrome, though by no means pathognomonic. They do occur in individuals who show no evidence of osteopsathyrosis. The blue color is not due to a deposit of pigment in the

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From The Department of Medicine, Duke University Hospital and School of Medicine.

sclerae but rather to scleral thinness and transparency which permit the choroidal pigment to be seen

6 It is probable that the relaxation of the ligaments of the bones of the middle ear is responsible for the deafness so frequently reported,² though labyrinthine⁵ and osteosclerotic⁶ deafness have been described

7 Upon electrical stimulation an incomplete reaction of degeneration is seen

8 Thinness and fragility of the hair and translucency of the teeth ascribed to a deficiency in enamel have been noted. Subjects of the disease are said to be especially liable to migraine and vasomotor disturbances of various types

9 The disease has repeatedly been observed in several generations. Apeit concludes that the malady is inherited in the manner of a Mendelian dominant character. There is a wide variation in the distinctive features in individual cases which may display any or all of them. Deafness, fragility of bone, or any other feature may be inconspicuous or absent in any given case.³ Blue sclerae may be the only apparent abnormality.⁷ Francke⁸ is of the opinion that the complete syndrome (blue sclerae, deafness, fragile bones) is found only in individuals whose parents have also shown it

In the light of the foregoing brief description of osteopsathyrosis the following case is reported

CASE REPORT

Luther C, a white male, aged 30, congenitally defective vision, blue sclerae, marked relaxation of ligaments producing pes planus and hypermobility of joints, blood chemistry normal, no fragility of bones

The patient entered the hospital on February 7, 1934, complaining of pain in the head and eyes of two years' duration

His father, mother and sister (the only sibling) were seen, and they state that no other member of the family has had any disease similar to that from which the patient is suffering. The parents state that the patient was not cyanotic at birth, nor could any evidence of rickets in childhood be obtained

Since birth the patient's sight has been exceedingly poor, and he was almost completely blind in childhood with some improvement as he became older. He was also born with a marked deformity of the left chest wall. As long as he can remember he has noted very marked looseness of all the joints, especially those of the knees and ankles. He has always had flat feet. Two years ago the right cornea was severely injured by a foreign body, reducing the very poor vision of the eye to a bare perception of light. All useful vision remaining exists in the left eye, where he can see only the gross outlines of objects

The patient presents a truly remarkable appearance (figure 1). He is very tall and thin with red hair and sharply contrasting indigo-blue sclerae. He looks older than his stated age of 30. The face is unusually long with a beak-like aquiline nose. The scapulae and acromial processes are very prominent, and there is marked anterior angulation of the left chest at the costo-chondral junction, producing a pigeon-breasted appearance

The extremities are unusually long, the hands flattened, and, owing to a remarkable grade of ligamentous relaxation, the tarsal bones (figure 2) have moved downward to such an extent that they lie at a lower level than the rest of the foot, being covered by a mass of hyperkeratotic skin. The joints everywhere show an extreme degree of relaxation and hypermobility. This is especially marked in the fingers, shoulder joints and knees



FIG 1 General appearance of patient



FIG 2 Showing marked relaxation of the ligaments of the knees and feet

The eyes show several noteworthy deviations from the normal (figure 3). The sclerae are really blue, not bluish. There are frequent nystagmoid jerks of the eye-balls, and it is then observed that the iris moves backward and forward in a wavy fashion as though having no anchorage from behind. No lens can be seen in either eye. The eyes show a definite divergent strabismus, and lateral movements cause nystagmoid jerkings. There is no evidence of injury to other cranial nerves except slight bilateral deafness by the audiometer test. Using air conduction, there was a loss of around 20 sensation units for both ears at all frequencies.

The lungs are negative, and the heart is not enlarged. There is a harsh systolic blow at the apex. The abdomen, genitalia and rectum show no abnormalities. The tendon reflexes in the upper extremities could not be obtained but are sluggish and equal in the lower extremities. Abdominals are present, Babinski bilaterally negative. No disturbance of sensation.



FIG 3 Showing appearance of eyes. Partial iridectomy has been performed.

Very exhaustive accessory clinical examinations were made. Blood studies, gastric analyses, kidney examinations, sedimentation tests, stool examinations, spinal fluid studies, etc., all gave normal findings. Complete blood chemistry studies in the laboratory of Dr. W. A. Perlzweig revealed no noteworthy deviation from the normal. The serum calcium and phosphorus were within normal limits on three examinations.

Numerous roentgen-ray studies were made, but, except for the malformations noted above, nothing abnormal in the bones was found. There was no marked decalcification anywhere.

Biopsy sections from a ligament of the foot (cuneonavicular) were made, and although there appeared to be looseness of the collagenous fibers as compared to similar normal tissue prepared in the same way, findings were not sufficiently striking to justify serious consideration.

The condition of the eyes was diagnosed by Dr. Banks Anderson as ectopia lentis. Both eyes were operated upon and later on maximum correction established, but the end result was poor, vision with the best possible correction being 15/200 in the left and 10/200 in the right eye.

SUMMARY AND DISCUSSION

A case is presented showing three of the cardinal features of osteopsathyrosis (Lobstein's disease, fragilitas ossium), but with no history or other evidence of bone fracture. The blue sclerae, defective ligaments and slight deafness (together with the finding of ectopia lentis) can all be explained by a congenital defect in the structure of fibrous tissue forming the sclerae, ligaments and tendons.

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 ORTHOSTATIC HYPOTENSION, REPORT OF A CASE

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IN 1926 Biadbuay and Eggleston¹ reported three cases of a syndrome, the outstanding characteristics of which were "the occurrence of syncopal attacks after or during exertion or even after standing erect for some minutes. Other features in the three patients are a slow, unchanging pulse rate, incapacity to perspire, a lowered basal metabolism and signs of slight and indefinite changes in the nervous system. Each of these patients felt much worse during the heat of summer." Other symptoms were increased urinary output when patients were in recumbent position, youthful appearance, and loss of sexual desire and power. A slight increase in blood nitrogen and lessened phthalein output when patients were up and active were also noted.

The most outstanding characteristic in all these cases was the abrupt drop in blood pressure when the patient changed from a recumbent to a vertical position. This drop involved both the systolic and diastolic pressures, the extreme figures being a drop in case 1 from 105 systolic and 60 diastolic supine to 40 systolic and 28 diastolic standing, in case 2 from 158 systolic and 108 diastolic to 52 systolic and 40 diastolic, and in case 3 from 84 systolic and 60 diastolic to 45 systolic and 25 diastolic. It was noted that the pulse rate was relatively slow and remained approximately the same even when the blood pressure sank to critical levels.

* Received for publication October 15, 1935

They designated this syndrome as "Postural Hypotension"

In 1928 Ghrist and Brown² reported two cases of this condition, Ashworth³ two in 1929, Reicke and Upjohn⁴ one in 1930, Barker and Coleman⁵ one in 1931, and Sanders⁶ one in 1931. In 1932 Laubry and Doumer⁷ reported five cases, two of which have been questioned as not representing the characteristic syndrome,⁸ and suggested the term "Orthostatic Hypotension" as being more descriptive than the one previously used. Barker⁸ reported an additional case in 1933, Allen and Magee⁹ one in 1934, Croll and Duthie¹⁰ one, the first in Great Britain, in 1935, Weis¹¹ one in February 1935, and in July of this year Alvarez and Roth¹² reported the eighteenth case (if we exclude the two questionable cases of Laubry and Doumer) thus emphasizing the rarity of the condition or, what is more probable, the infrequency of its recognition.

The normal reactions of blood pressure and pulse rate to postural change have been studied by many investigators. In general, on changing from a horizontal to a vertical position there is slight elevation or depression in the systolic pressure, a definite rise of about 10 millimeters in the diastolic pressure, resulting in a lowered pulse pressure and a definite increase in pulse rate amounting to 10 or more beats per minute.

REPORT OF CASE

History C. W., a white male, school teacher, aged 56, was of Irish-Dutch extraction, of a family noted for longevity, the second of a family of nine children all of whom are living except two, an all-round college athlete (football, baseball, track and tennis) actively engaged in athletics up to the age of 45. He had always been healthy until the onset of the present condition except for minor ailments and except for a ligneous abscess behind the right ear at the age of 30 and an attack of iritis of the left eye at 39.

In August 1928, he was first troubled with frequent urination at night. Several doctors reported a few pus cells in the urine. He had several teeth extracted (one ulcerated) without relief. In October the urinary disturbance became more pronounced. In April 1934, he passed a large rough stone, preceded by passage of bloody mucous in urine. From 1928 to 1934 he drank artesian water of high mineral content. Prior to this time he had always perspired freely, but during this period it gradually ceased, and he perspired only from mid-chest up. Perspiration gradually ceased almost completely until the spring of this year when he perspired somewhat more freely. He did not note that he was particularly intolerant to hot weather.

In the fall of 1934 he noted a burning sensation across the abdomen, extending down to the feet and corresponding roughly to the area of anhidrosis. In January 1935, he had an attack of influenza, and after this the burning sensation mentioned above ceased and, as the weather became warmer, he began to perspire more freely.

About three years ago he began to note muscular weakness and fatigue about the hips. At first this was intermittent. He also noticed a similar weakness in the arms but much less marked, the symptom disappearing quickly with rest. About this time he began to "stoop" or "hump over" in walking, and his friends would tell him to "straighten up." A little later he would become very tired through the hips after walking a block or two, finding it necessary to rest after slight exertion. At the time he attributed this to the fact that he had sustained a fracture of the hip at football. Soon this localized fatigue became general all over the body and progressively worse, until now he experiences profound fatigue, giddiness and almost faints on changing from reclining to upright position, walking, and particularly on standing still for a few moments. Associated are fatigue and cramping in the muscles of the

legs, arms and neck. The muscles of the neck became so weak he could scarcely hold his head up, and this has become one of the most pronounced symptoms. The vocal cords would become fatigued and the voice husky and uncontrollable. The muscles of the arms seem too weak to lift any weight. These symptoms are most pronounced when he is standing, are relieved somewhat when he sits down, and he experiences prompt and almost complete relief when he lies down.

More recently he has experienced blurring of vision when standing or after exercise, promptly relieved by sitting down, bending forward or reclining.

He has noticed coldness of lower extremities below the knee for the past year, and since last winter he has noticed swelling of the feet and ankles. This has lately disappeared. There has been some numbness and tingling.

He passes very little urine during the day when he is up and around, but has nocturnal frequency and polyuria. Actual test after treatment was under way showed 12.5 ounces for the 14.5 waking hours, and 20 ounces for the 9.5 sleeping hours.

He has developed nervousness, a coarse tremor of the hands, and more or less mental sluggishness. He has also developed peculiar involuntary movements resembling laughter. This is more pronounced when he is weakest. He has also developed some emotionalism. There has been loss of sexual desire and potentia.

He came to me first on August 2, 1935, with this story and the diagnosis of heart trouble and low blood pressure.

Examination, August 2, 1935. A well developed and well nourished middle-aged white man, apparently not as old as stated age. Temperature 99.2° F, pulse 84, blood pressure reclining 120 systolic and 80 diastolic. There is no apparent anemia, cyanosis, jaundice, edema, dyspnea or distress. The face is rather florid, the beard somewhat thinner than in the average man, the hair graying, and a tendency to baldness. The eyes, ears, nose, mouth, teeth, tongue and pharynx show no significant changes. The thyroid is not enlarged and there is no cervical adenopathy.

Heart shows slight enlargement to the left. There are no murmurs or abnormal accentuations. The heart tones are normal. Lungs. No abnormal findings. Chest wall. No abnormality. Abdomen. No abnormality noted. The liver and spleen are not palpable. No areas of tenderness, and no masses to be felt. Genitalia. No abnormality found. Rectal. Negative findings. Neuro-muscular system. The musculature is apparently normal. There is a definite coarse tremor of the fingers, more marked in the left hand. Tendon and superficial reflexes normal. Pupillary reactions are also normal. Integument. The skin is soft and pliable. There are no evidences of pigmentation. There is no obvious perspiration.

Blood. hemoglobin 90 per cent Sahli, red blood cells 4,510,000, white blood cells 6,100. N 67 per cent, L 33 per cent. Sugar tolerance after 100 grams of glucose, 80-150-125 mg. Wassermann and Kahn negative. NPN 510 mg. Urea N, 26.7 mg. Phthalein output reduced, although he collapsed and voided involuntarily 20 minutes after intravenous administration of the dye. For the balance of the two hours the elimination was 25 per cent.

As stated above, the blood pressure at the first examination was 120 systolic and 80 diastolic with patient in recumbent position. Upon sitting up an immediate drop to 95 systolic and 70 diastolic was noted. The following day I rechecked the blood pressure and found the following: recumbent, 125 systolic and 80 diastolic, sitting, 90 systolic and 60 diastolic, standing, 60 systolic and 7 diastolic, with weakness and syncope. During these observations the pulse rate was around 80, and varied scarcely at all from this figure, even when pressure went to extreme low levels. I have made many blood pressure observations always with the same general results, namely, a marked drop in both systolic and diastolic pressures upon changing from horizontal to vertical positions, with little or no change in the pulse rate. Typical are the observations made on August 28, 1935, and checked with Dr. W. F. Keller. (Figure 1.)

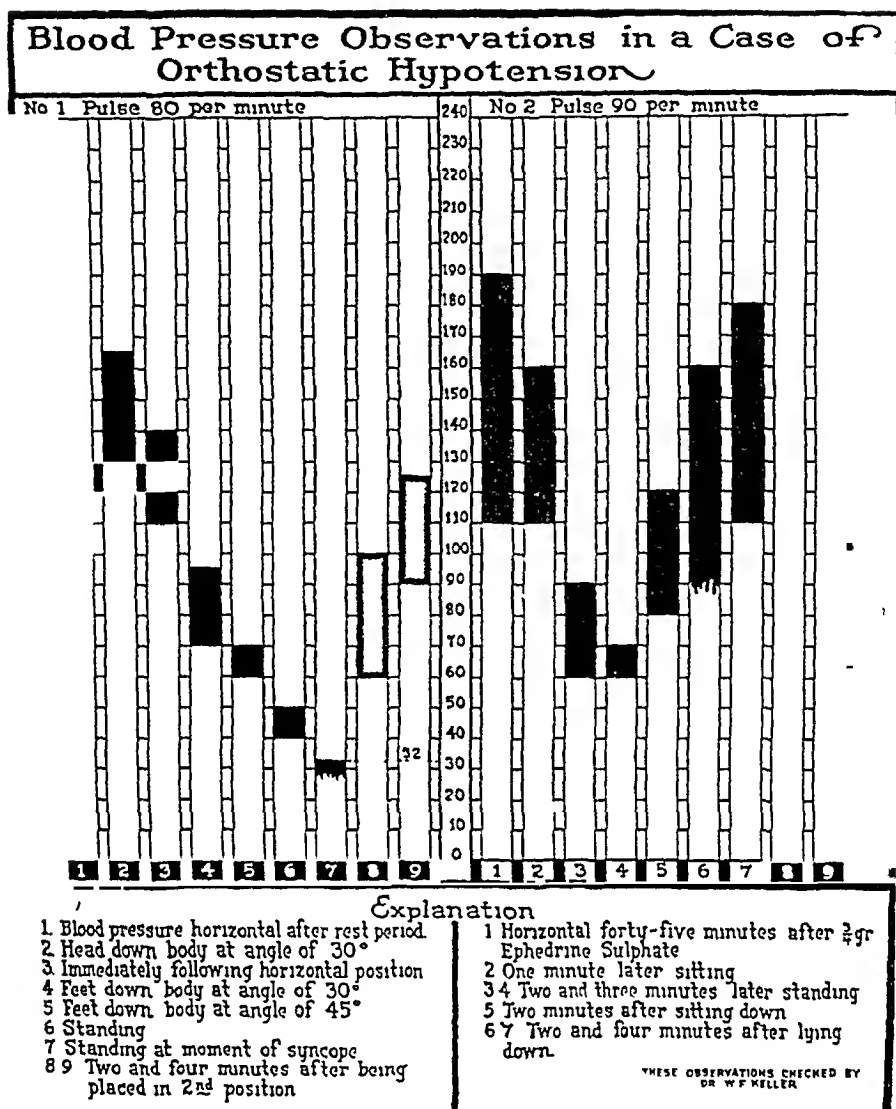


FIG 1

The following observation noted on different occasions, to me is unique and perhaps important. During attacks of great weakness the patient has involuntary paroxysms exactly simulating laughter, during which he chuckles and manifests the typical contractions of the abdominal muscles, but he feels no desire to laugh and the facies indicates no emotion of amusement. When a normal individual laughs the blood pressure is raised, when this man has such a paroxysm his pressure is raised. Ghrist and Brown in one of their cases noted what may be an analogous phenomenon, namely, clonic convulsions just preceding syncope, explained by the patient as being voluntary muscular contractions in an effort to stand.

To summarize the case. An apparently healthy middle-aged man presents certain definite subjective and objective findings, namely, orthostatic drop in both systolic and diastolic pressures without compensatory increase in pulse rate,

orthostatic weakness, giddiness and syncope, orthostatic oliguria, increase in blood urea nitrogen, with reduced phthalein output, hypohidrosis with geographic distribution, loss of libido and potentia, nervousness, tremor, and involuntary convulsive paroxysms resembling laughter when very weak—all of the characteristic findings of the syndrome designated as orthostatic hypotension.

An analysis of the cases thus far reported is shown in the following table. This reveals orthostatic hypotension and orthostatic weakness, giddiness and

SIGNIFICANT FINDINGS IN CASES REPORTED

Symptoms

Symptom	Positive	Negative	Doubtful	This case
Orthostatic severe syncope	11	7	0	+
Orthostatic weakness or mild syncope	17	1	0	+
Orthostatic oliguria	10	0	8	+
Anhidrosis or hypohidrosis	10	3	5	+
Intolerance to hot weather	4	2	12	0
Loss of libido and potentia	3	5	10	+

Physical and Laboratory Findings

Finding	Positive	Negative	Doubtful	This case
Orthostatic hypotension	18	0	0	+
Slow or unchanging pulse rate with changing position	12	4	2	+
Lowered metabolic rate	10	2	6	?
Increased blood urea nitrogen	7	0	11	+
Youthful appearance	4	7	7	+
Slight anemia	5	6	7	0

syncope as invariable phenomena, and lack of compensatory tachycardia, lowered metabolic rate, nitrogen retention, and orthostatic oliguria, as almost invariable.

In addition to the above practically constant findings, others of greater or less significance are changes in the pupillary reactions, and other neurological changes, insomnia, weight loss, dyspnea, geographic anhidrosis, etc.

Bradbury and Eggleston found that the administration of epinephrine was followed by an increase in systolic and pulse pressures and in pulse rate, but that the diastolic pressure was not materially affected. They concluded that epinephrine did not cause vaso-constriction in these cases. Atropine caused dryness of the mouth and flushing of the skin in two cases, but no increase in

pulse rate. Pilocarpine caused salivation and sweating in two cases. In general, these observations have been confirmed by other investigators. Bradbury and Eggleston conclude that "paralysis of the sympathetic vaso-constrictor endings seems to be the only adequate explanation of the blood pressure reactions in these three cases. It accounts for the absence of vaso-constriction following the injection of epinephrine and it explains the total absence of the normal vasomotor control by which blood pressure is maintained at a nearly constant level in the face of changes in the position of the body in normal persons." In general, these conclusions have been concurred in by subsequent authors. Ghrist and Brown thought that "the essential disturbance in this disease is lack of resistance in the splanchnic vessels to shifts in the blood mass and absent or diminished vagus regulation of the heart rate to changes in blood pressure. The opinion is advanced that this disease represents a hypotonic state of the myoneural structures of the sympathetic and parasympathetic nervous system of unknown origin." Barker explains these phenomena 'by loss of reflex posture or orthostatic vaso-constriction necessary to maintain normal blood pressure against the force of gravity and by loss of reflex acceleration of the cardiac rate.' He attributes the accelerator effect of epinephrine and ephedrine in these cases to their direct effect on the heart muscle. Alvarez and Roth believe the essential pathological physiology is in the "sympathetic control of the caliber of the vessels in the abdomen."

Prof J. A. MacWilliam, who studied the case of Croll and Duthie, found that in normal individuals "the slower heart rate in the horizontal posture, as compared with the sitting is essentially due to the action of the carotid sinus reflex, while the quicker rate in standing than in sitting is mediated through afferent impulses from the lower limbs which are also concerned in the maintenance of the compensatory adjustments (vaso-constriction in the splanchnic area and elsewhere) involved in keeping up the aortic pressure in the erect posture." He believes that "both pulse rate and blood pressure adjustments in the standing posture are influenced by afferent impulses from the lower limbs, apparently originating in some part of the vascular circuit in these limbs," and that in these cases there is a disturbance of this mechanism, an opinion that seems to be refuted by Alvarez who points out that while orthostatic hypotension is not produced by lumbar sympathectomy, it is produced for a time by anterior rhizotomy.

Alvarez and Roth also found that epinephrine intravenously did not cause peripheral vaso-constriction, although it did cause elevation of pulse rate and systolic blood pressure. The fact that atropine does not cause increase in pulse rate in these cases suggests interference with the normal sympathetic accelerator mechanism of the heart. On the other hand the sympathetic supply to the sweat glands is intact if depressed since the reaction to pilocarpine is present to an extent at least.

The effects of various therapeutic agents have been observed. Epinephrine, in addition to raising the systolic pressure and pulse rate, gave temporary symptomatic relief. Thyroxine gave questionable relief in the work of Bradbury and Eggleston. The use of a tight abdominal binder has given variable results in different patients. Ghrist and Brown first noted the beneficial effects of ephedrine. Barker, and later Allen and White noted improvement from ephedamine tartrate, but the disagreeable symptoms seemed to more than counterbalance the

benefits. Various other remedies have been tried, but to date ephedrine sulphate seems to have given most consistent and lasting improvement subjectively and objectively.

Having noted the beneficial effects of suprarenal cortical hormone (eschatin) in a case of Addison's disease with orthostatic hypotension (secondary), I decided to try this remedy with my patient, and accordingly on August 3, I gave him 1 cc intramuscularly and he reported that within an hour or two he felt stronger. I repeated this on August 4, omitted it on the fifth, and on the morning of the sixth he collapsed in the elevator on his way to my office. I gave him 5 cc of eschatin immediately and within 30 minutes the blood pressure was 150 systolic and 100 diastolic, with patient recumbent. The following day he was feeling better, the blood pressure being 160 systolic and 100 diastolic reclining and 120 systolic and 80 diastolic sitting, in the forenoon, and in the afternoon, after some walking during the interval, 125 systolic and 90 diastolic sitting. I did not repeat the eschatin on this date.

On the morning of August 8 he took $3/8$ gr ephedrine sulphate and reported to the office at 9 00 o'clock. At this time his pressure was 120 systolic and 80 diastolic reclining, and 90 systolic and 60 diastolic sitting. I gave 0.25 cc eschatin and in 20 minutes the reading was 150 systolic and 100 diastolic, reclining. On the ninth he received 0.25 cc and on the tenth when he reported the pressure was 90 systolic and 60 diastolic, and he complained of weakness. I gave him 0.5 cc with only slight improvement. From August 10 to August 21 he took $1/3$ cc eschatin and $3/4$ gr ephedrine sulphate daily and though his condition was better than before he began treatment, it was far from being satisfactory. He noted that the ephedrine invariably caused increased pulse rate, heart consciousness and nervousness. He reported on the twenty-first, with the following blood pressure: 125 systolic and 80 diastolic, reclining, 90 systolic and 60 diastolic, sitting. At 3 00 o'clock p.m. it was 100 systolic and 70 diastolic and 60 systolic and 40 diastolic. I gave him 0.5 cc eschatin and in 30 minutes the pressure was 140 systolic and 90 diastolic, and 100 systolic and 60 diastolic sitting. From the twenty-first to the twenty-seventh, ephedrine was omitted and 0.5 cc eschatin twice daily was administered. He was fairly comfortable during this period but experienced considerable weakness. He reported on August 28 when the series of observations charted was made.

From August 28 to September 3 he took ephedrine and amylal three times a day, but the cumulative effect of the amylal was too disturbing. I then outlined a course of procedure whereby he took one-half grain of ephedrine before getting up in the morning and one-fourth grain every four hours during the day. He felt, however, that the larger dose in the morning was unnecessary, he has settled down to three or four one-quarter grain doses daily, and his condition has been much more satisfactory.

Although Weis has reported a case as cured by this therapy, and his observations over a considerable period of time seem to substantiate it, it seems too much to expect a cure in this case, although one hopes to make life livable for him.

Weakness, dizziness, faintness, a tendency to syncope on suddenly changing from a reclining to an upright posture or upon standing still for a few moments, are not uncommon complaints. If every such case were carefully considered and blood pressure readings made in both positions, it is entirely possible that many other cases might be recognized. In view of the frequency of anhidrosis or hypohidrosis in these cases, all patients complaining of this symptom should be investigated with this entity in mind.

One occasionally sees individuals, usually of a definite ptotic type with low blood pressure, who have been improved apparently by the use of a tight abdominal binder. Improvement is not due to replacement of the abdominal viscera, for some of us have demonstrated with the fluoroscope that this does not occur in spite of the symptomatic improvement. A study of this case and of the reports of others leads one to believe that any such benefits come from forcing the blood out of the splanchnic area, and that in all probability in some of the cases at least the symptoms are due to splanchnic vascular atonicity.

Certain acute processes, notably influenza, affect blood pressure. Is it not probable that some of the profound debility in influenza may be on the same basis?

SUMMARY

1 There appears to be a definite entity with characteristic findings which may be properly designated as orthostatic hypotension.

2 The chief characteristics are orthostatic hypotension, orthostatic weakness or syncope, absence of compensatory tachycardia on rising from reclining to upright position, orthostatic oliguria with nitrogen retention and decreased phthalin output.

3 The syndrome seems to be on a basis of sympathetic nerve ending impairment.

4 The literature has been reviewed briefly.

5 Eighteen cases have been reported previously and another is presented here.

6 To date ephedrine sulphate has given most consistent benefit.

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COMPLETE HEART BLOCK FROM SCLEROSIS OF THE BUNDLE OF HIS

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COMPLETE heart block may result from various types of lesions involving the bundle of His or other parts of the conduction system. Most of the cases of complete heart block reported in the literature were the result of syphilitic gummas. There are on record isolated cases of heart block in which fatty infiltrations have caused auricular-ventricular dissociation, in others, tumors, such as endotheliomas and sarcomas, have been found to destroy the conduction pathways of the bundle. On the other hand, there are numerous cases in which there was clinical heart block, but at autopsy no lesion was found in the bundle of His.

In a recent paper, Yater and Cornell supply evidence which indicates that heart block may be due to calcareous lesions involving the bundle of His, as well as the subendothelial surface of the heart. Yater further states that this specific form of lesion producing complete heart block must be rare, as he could find only 47 cases which have been sufficiently studied and in which the criteria fulfilled the requirements for this diagnosis. It is possible that this condition may be much more frequent than the literature leads one to believe. On account of the rarity of complete heart block due to calcareous disease of the bundle of His, we present this report with the hope that it may stimulate a search for similar cases.

CASE REPORT

Case History An unemployed Italian male, aged 62, was admitted to Touro Infirmary, on the service of Dr Emile Block, June 3, 1934 and died June 9, 1934. The patient was referred to one of us (B R H) within 20 hours after admission, with a history that his present illness started three weeks previously. Predominating symptoms were marked dyspnea, swelling of the ankles, and inability to sleep at night. All symptoms were progressive in character until the occurrence of abdominal swelling, which had been present for one week. During this period there was precordial pain, running down the arms, later there was a productive cough.

Physical Examination Examination revealed a well-developed male, of large frame, with moderate cyanosis and generalized edema. Dyspnea was unusually marked. The heart was markedly enlarged to the left. The apex impulse was easily seen and felt at the anterior axillary line on the left side. The right border extended outward about 5 cm from the median line in the third interspace. The cardiohepatic angle could not be made out, the impression was gained that there was a pericardial effusion, although the classical signs were absent. The heart sounds were feeble, especially at the apex, while at the base they were more easily audible. The pulse and heart rate, while the patient was lying down, was 30 per minute. The peripheral vessels were moderately sclerosed. The blood pressure was equal on both sides, being 215 systolic and 110 diastolic. The lungs showed fine crepitations at both bases. The liver was markedly enlarged downward and very tender. There was free fluid in the abdomen as shown by shifting dullness.

* Received for publication October 5, 1935.

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Our impression of the case was atherosclerotic type of heart disease with hypertension, congestive heart failure, complete heart block, and general anasarca.

An electrocardiogram taken shortly after entrance into the hospital (figure 1) revealed heart block of high grade, with infrequent ventricular extrasystoles. A

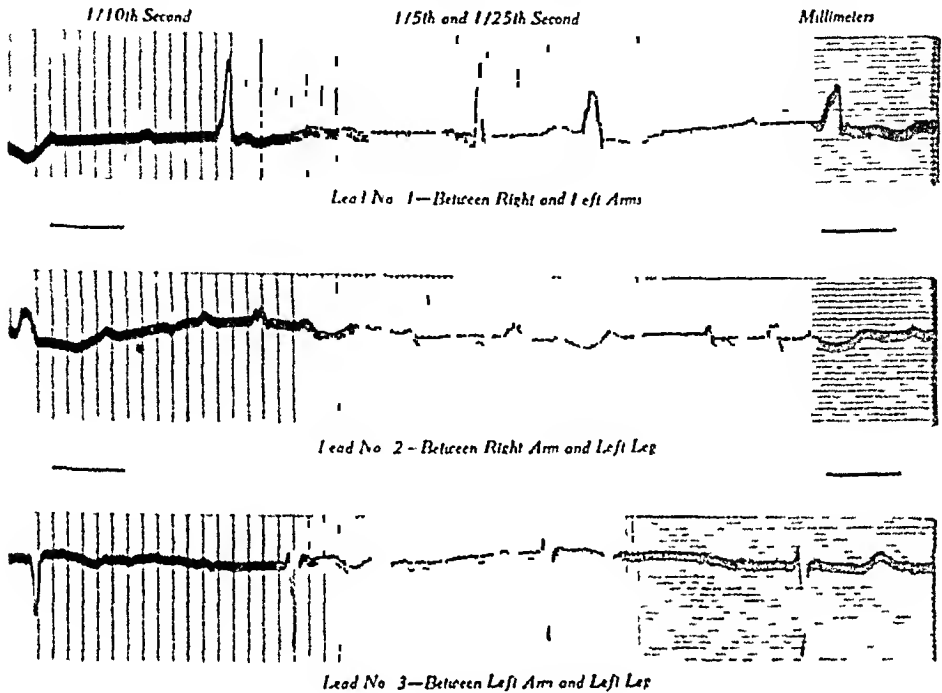


FIG 1

second cardiogram taken 6/5/34 revealed about the same picture, the ventricular rate in both was 30 to 45 per minute.

Progress Notes The patient was placed on the conventional treatment for congestive heart failure, including limitation of fluids, a salt-poor diet, and digalein, 2 cat units every four hours for a period of three days, totaling 24 cat units. Following this digitalization, there seemed to be definite improvement, the area of cardiac dullness apparently diminished, there was less orthopnea, and the mental attitude of the patient was very noticeably improved. Following the discontinuance of digitalis the apparent improvement was maintained for about 30 hours, but then the dyspnea returned in even more marked degree. With this, the patient seemed to develop mental disturbances, in that he was unwilling to remain in the hospital. Finally, smothering spells became so distressing that the patient could hardly be kept in bed. Morphine with atropine was given hypodermically without much benefit. Suddenly, while the patient was sitting up in bed, he developed convulsive seizures. The pulse varied from 28 to nearly 50 per minute. Barium chloride, gr 1 every three hours, was given for the next 24 hours, but in spite of this, repeated convulsions ensued, lasting for variable periods of time. The patient died suddenly on the morning of June 9, 1934.

Pathological Examination Gross Examination of the Heart and Pericardium. The pericardium was smooth and glistening. There were approximately 75 cc of clear amber-colored fluid in the pericardial sac. The heart weighed 460 grams and showed hypertrophy of the left ventricle. There was a moderate amount of fatty infiltration evident beneath the epicardial surface. The organ was removed and

sectioned. The myocardium was reddish-brown in color and measured 3 cm in thickness. Scattered throughout it were areas of degeneration. The endocardium was pinkish-gray in color, smooth and glistening in appearance. The foramen ovale was closed. All valves were competent. The ostia of the coronary arteries were patent, however, upon tracing the arteries they were markedly sclerotic. The in-



FIG 2 View of left ventricle and aorta. Calcium mass (C) shown diagrammatically in approximate position after blocks in area, B, have been taken out. Area S indicates where a further section was removed for study of the muscular septum. Arrow points to the right coronary artery orifice.

timal surface of the aorta was pinkish-yellow in color, with many arteriosclerotic plaques scattered throughout.

Histopathologic Examination of the Heart Two blocks of tissue were removed from the heart at the junction of the membranous and muscular septum. These blocks were taken so as to include an area from the bases of the right and left anterior aortic valves to within about 1 cm of the muscular septum of the heart. Microscopic sections were taken at various intervals so as to determine the length and distribution of the fibro-calcareous mass, A-V bundle and its branches. Figure 2 shows the opened left ventricle and aorta with area from which the blocks for examination were taken. An additional section was taken from the muscular septum for study of the A-V bundle and its branches. The arrow points to the right coronary artery, thus giving exact anatomical location of the blocks. The approximate location of the calcareous mass is indicated diagrammatically.

The tissues were partially decalcified and sections cut at 10 micra. The sections were stained with hematoxylin and eosin and with Mallory's connective tissue stain. Sections were taken from various regions and approximate length of the mass was ascertained. Figure 3 reveals the position of the mass and its characteristic nature. Figure 4 is a higher magnification of a portion of figure 3.

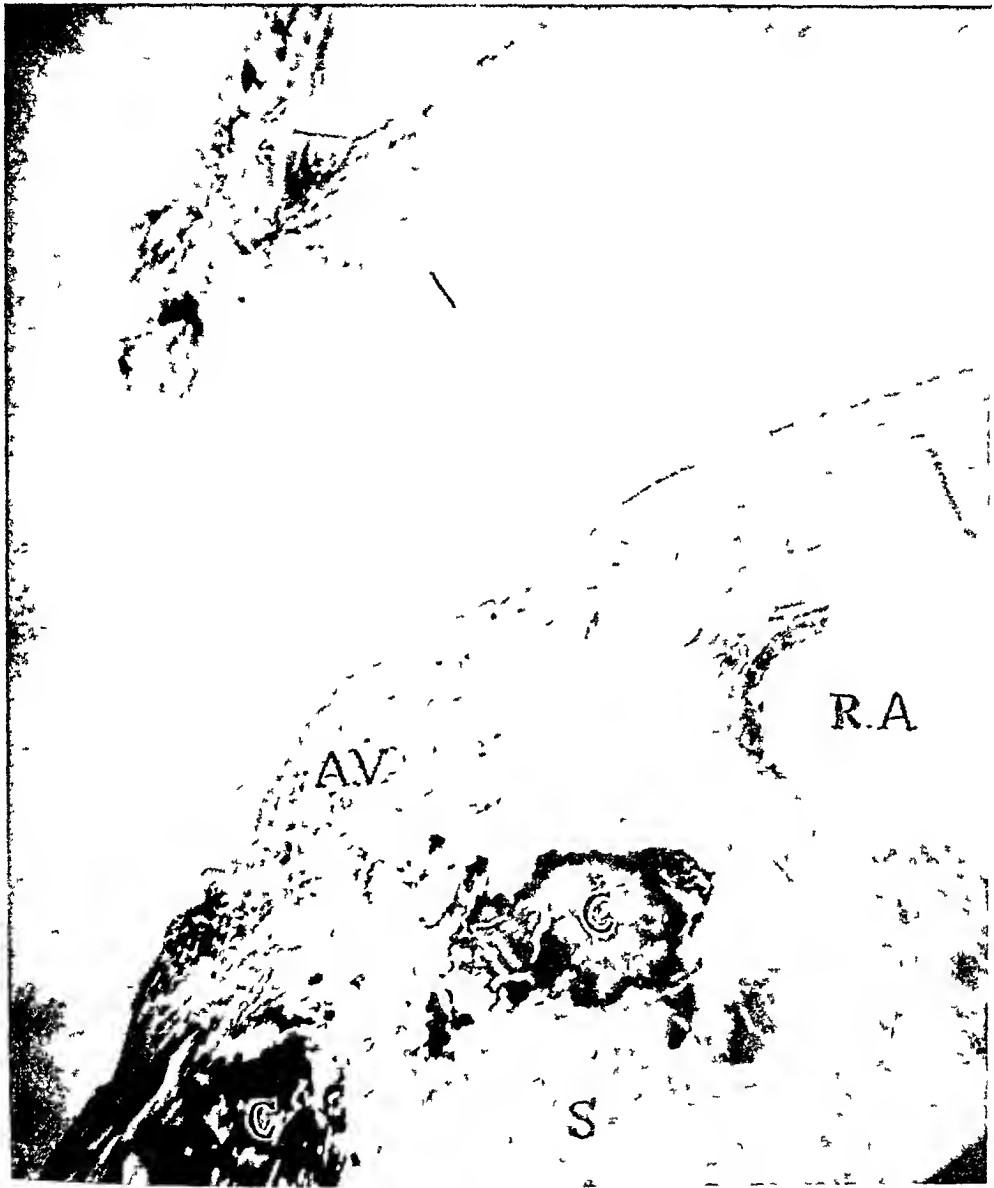


FIG 3 Low magnification of membranous and muscular septum revealing the exact position of the calcium mass. *RA* is right auricle, *A-V* indicates the atrio-ventricular bundle, *C* indicates the two calcium masses with small particles of the homogeneous substance scattered between. An edge of the aortic cusp is shown above. *S* indicates the muscular portion of the septum. (45 \times mag.)

A calcareous mass was revealed at the junction of the membranous and muscular septum in the myocardial portion, which was surrounded by dense fibrous connective tissue. Near the center of the mass this fibrous connective tissue separated the cal-

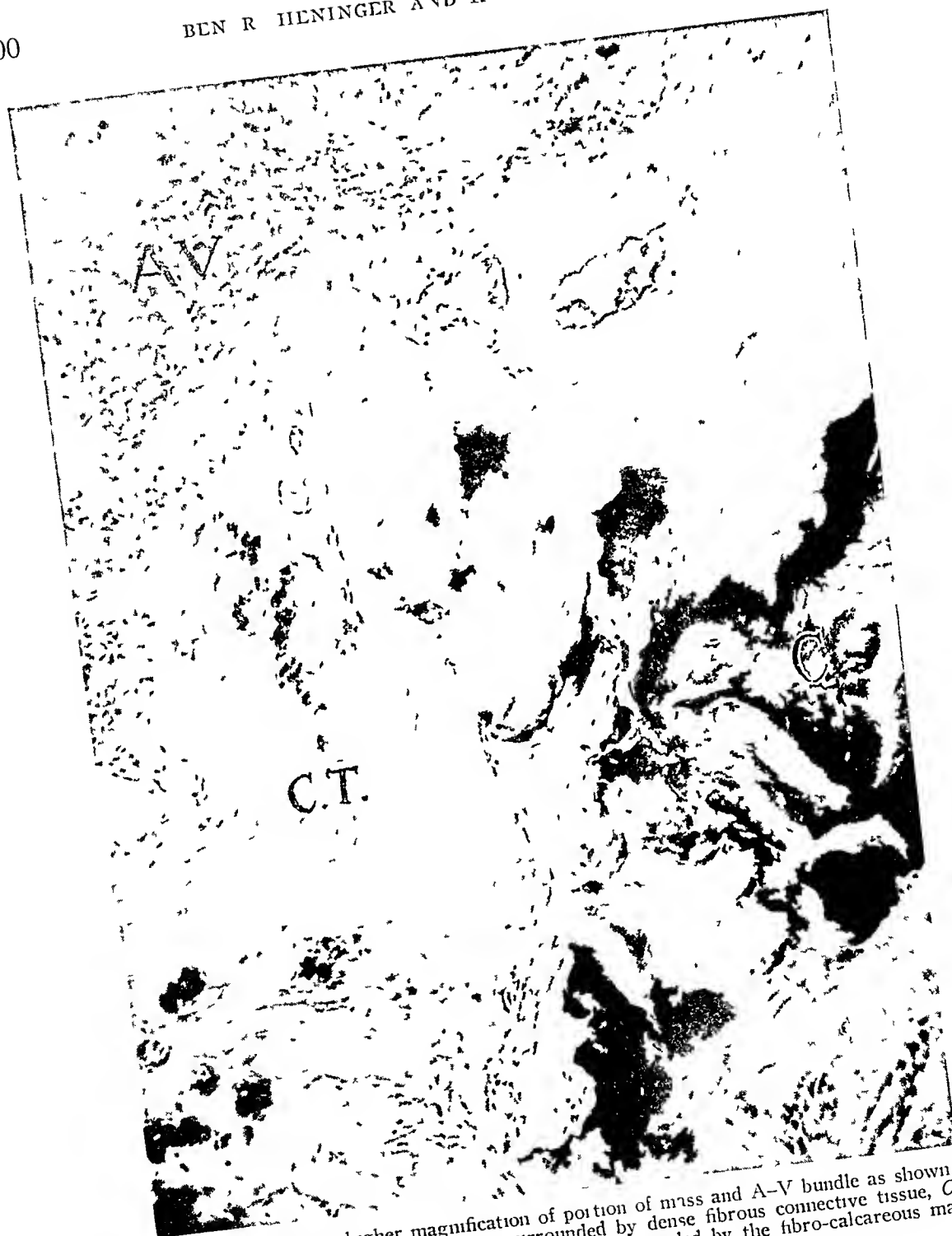


FIG 4 Reveals a higher magnification of portion of mass and A-V bundle as shown in figure 3. C indicates the calcium mass surrounded by dense fibrous connective tissue, CT, AV bundle (A-I) is seen being impinged upon and invaded by the fibro-calcareous mass (100 \times mag)

calcereous mass into two parts. Each mass measured approximately 1.5 mm. in diameter and 6 mm. in length. Near the ends of the mass it became smaller and narrower and finally disappeared. The mass ran parallel to the base of the aortic leaflet of the mitral valve (figure 2). The mass was largely on the left side of the septum, it impinged upon the A-V bundle near the center and at some places was seen to invade the bundle substance. Small portions of calcified material were seen scattered around the main mass. The A-V bundle and its branches were apparently normal in cellular structure throughout. There were a few lymphocytes in and around the mass.

The muscular septum was quite hypertrophied as were the individual muscle cells. There were no endothelial changes of note and conduction system was apparently normal in cellular structure. The aortic valves showed evidences of slight calcification in their bases, but were otherwise competent. A number of small arteries around the calcified mass showed definite sclerotic changes but none were completely obliterated. The coronary arteries were definitely sclerosed. The photograph of the heart and photomicrographs further add to this description.

We wish to express our appreciation to Dr. John S. Lantford, Director of the Department of Pathology, Toussaint Infirmary, New Orleans, who performed the autopsy.

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EDITORIAL

CUSHING'S SYNDROME AND TUMORS OF THE ADRENAL CORTEX

IN 1932, Cushing¹ published an account of the syndrome which now goes by his name and which he called pituitary basophilism. As is well known, he was able to collect a group of cases associated with basophilic tumors of the hypophysis, all of which showed some or many of the following characteristics: adiposity of the face, neck, and trunk, the extremities not being affected, vascular hypertension, hirsuties, particularly of the face and trunk in females, impotence or amenorrhea, cyanosis and edema of the extremities, a tendency to polycythemia, with a florid or plethoric complexion, dryness of the skin, often with acne, and particularly with purplish lineae atrophicae, osteoporosis, glycosuria or albuminuria, and variable backache, weakness, and fatigability. Other cases were soon reported, but it became evident that such a syndrome might also occur in the absence of a pituitary tumor, associated with other endocrine lesions particularly of the suprarenal cortex and thymus^{2,3}. Pituitary basophilism, therefore, or a syndrome which cannot be distinguished from it, although frequently accompanied by a pituitary growth, is not invariably so related. Examination of a large number of pituitary glands by Costello,⁴ with serial sections, in cases where no endocrine disturbance was obvious clinically, also indicated that such tumors were to be found in the absence of the symptoms which have been described.

Studies recently reported by Crooke⁵ may have fundamental importance in throwing light upon this problem. He has discovered that a hyaline change is present in the basophilic elements of the anterior pituitary, often with cellular distortion, and with a diminution in the number of basophilic granules present, in cases of pituitary basophilism. The lesion is not found in the basophilic adenomata when present, but only in the proper glandular tissue. This change was found not only in cases of Cushing's syndrome with basophilic adenoma of the pituitary, but also in similar clinical disorders in which neoplasms of the thymus, or growths or hyperplasia of the adrenal cortex, were the conspicuous lesion, and in which a basophilic pituitary

¹ CUSHING, H. "Dyspituitarism" 20 years later, with special consideration of pituitary adenomas, *Arch. Int. Med.*, 1933, li, 487-557. Basophile adenomas of pituitary body and their clinical manifestations (pituitary basophilism), *Bull. Johns Hopkins Hosp.* 1932, l, 137-195.

² LESCHER, F. G., and ROBB-SMITH, A. H. T. Comparison of pituitary basophilic syndrome and adrenal cortico-genital syndrome, with report on pathology, *Quart. Jr. Med.*, 1935, iv, 23-35.

³ LEYTON, O., TURNBULL, H. M., and BRATTON, A. B. Primary cancer of thymus with pluriglandular disturbance, *Jr. Path. and Bact.*, 1931, xxxiv, 635-660.

⁴ COSTELLO, R. T. Subclinical adenomas of pituitary body, *Proc. Staff Meet., Mayo Clinic*, 1935, x, 449-453.

⁵ CROOKE, A. C. Change in basophile cells of pituitary gland common to conditions which exhibit syndrome attributed to basophile adenoma, *Jr. Path. and Bact.*, 1935, xli, 339-349.

adenoma was not found after most careful search. All of these cases suffered from hypertension, as did those described by Cushing. Crooke believes this hyaline change in the basophiles is an expression of altered physiological activity rather than a degenerative change in the ordinary sense. He has also made interesting observations on the pituitary in Addison's disease, where extreme reduction in the number of basophiles and the presence of abnormal basophilic transitional cells are to be found. Nicholson⁶ has reported recently a difference in the histologic picture in pituitary glands from patients with Addison's disease due to cortical atrophy and those due to tuberculosis. Only in the first group was he able to show reduction in the number of basophiles and the appearance of abnormal basophilic cells. Crooke suggests that this reduction in these elements is associated with the cause of the hypotension and perhaps of the hypoglycemia which are found. Since cortical hormone therapy in Addison's disease does not seem to influence this pituitary lesion, a plausible reason is afforded for the slight effect which it also has on the clinical course of the hypotension.

Other relationships of the adrenal cortex are indicated, however, by certain cases of cortical tumor which instead of being associated with Cushing's syndrome exhibit the even more striking clinical phenomena of stimulation or reversal of sex. In this they seem to show a sharp difference from the first named condition, in which the characteristic sex changes are those of inhibition or depression rather than of virilism. There is, however, considerable uncertainty as to just how clear a distinction may be drawn between the two conditions. If a hormonal principle, elaborated by the tumor cells, is responsible for the sex changes as seems altogether likely, it would appear to be more closely related to the gonads than to the pituitary. Removal of the tumor, in a number of brilliant instances, has resulted in practical cure of the patient, with disappearance of the abnormal sex phenomena.⁷ It seems probable that the salt and water hormone of the adrenal cortex, which is to a certain degree effective in Addison's disease, has nothing to do with this sex reversal or sex stimulation, at least not in any clear and direct way. This is, of course remarkable, since the methods of extracting this material, by means of lipid solvents, are precisely those which have been found so effective in the isolation of the gonadal hormones. Hartman has, indeed, reported a separate lactogenic principle from the adrenal cortex.⁸ The evidence available, therefore does seem to suggest that more than one hormonal principle may be present in the adrenal cortex.

The closely related embryological origin of adrenal cortex and gonads, within the genital ridge, and the occurrence of the "X" layer between reticularis and medulla in embryonic life, are circumstances undoubtedly of great significance. The presence of this layer is believed to be responsible

⁶ NICHOLSON, W. M. *Bull. Johns Hopkins Hosp.*, 1936, LVIII, 405.

⁷ WALTERS, W., WILDER, R. M., and KEPIER, E. J. Suprarenal cortical syndrome with presentation of 10 cases, *Ann. Surg.*, 1934, c, 670-688.

⁸ BROWNELL, K. A., LOCKWOOD, J. E., and HARTMAN, F. A. Lactation hormone of adrenal cortex, *Proc. Soc. Exper. Biol. and Med.*, 1933, XXX, 783-784.

for the relatively great size of the fetal adrenal. At one period of gestation it equals the kidney in size, and at birth it is still one-third the size of the latter organ.⁹

Much of the accessory cortical tissue, particularly that in association with the reproductive organs, may well be a part of this tissue, a glandular entity, quite distinct in function from the rest of the cortex. Its involution normally begins soon after birth and is nearly complete at the end of the first year. A thin juxta-medullary zone of pigmented cells is said to persist in the adult and may be a remnant of this involuted tissue. Hypertrophy or persistence of portions of it which have not undergone involution, according to one theory, may be responsible for the adreno-genital syndrome associated with tumors of the cortex. Broster and Vines¹⁰ report the occurrence of bright red granules, upon staining with Ponceau-Fuchsin, in the cytoplasm of adrenal cells of the reticular layer in such tumors, and find that they are also normally present in the "X" layer of embryonic life. If confirmed, such a finding would point to the undue persistence of cells from this layer into later life as one causal factor in the production of these conditions of sex reversal and stimulation. Others, however, have not been so fortunate in the demonstration of this staining reaction, and its regular occurrence in these cases is as yet not certain.

This recent evidence for the occurrence of two types of adrenal cortical tissue, quite different in their physiological significance, constitutes a new and probably an important advance in our progress toward a final solution of the problem of adrenal function.

⁹ GROLLMAN, A. The adrenals, 1936, Williams and Wilkins, Baltimore.

¹⁰ BROSTER, L. R. and VINES, H. W. C. The adrenal cortex, a surgical and pathological study, 1933, Lewis, London.

REVIEWS

Textbook of Psychiatry By ARTHUR P. NOYES M.D. Second Edition 329 pages, 15 X 22 cm Macmillan Co., New York 1936 Price, \$2.50

Dr. Noyes offers a revised edition of his popular textbook which found such wide acceptance when first issued in 1927.

It is primarily intended for nurses, but presents one of the best simple understandable expositions of mental mechanisms and psychiatric reaction types that we know. It is in no sense exhaustive. It is designed to give the nurse some idea of what mental disease is and a brief picture of the symptoms occurring in various types of mental reaction.

The first nine chapters are devoted to dynamics of normal and abnormal behavior and to explanation of accepted American theories as to the causes underlying emotional disorders. Most of the rest of the book devotes itself to description of clinical pictures as typically found. At the end of each clinical picture there is a short section called "Nursing Management" which gives practical suggestions as to things which the nurse can actually do to protect and help her patient. At the end of the book there is a good chapter called "Psychiatric Nursing" and a brief survey of the author's views on psychoanalysis and mental hygiene. The book ends with a fairly complete glossary of the commoner psychiatric terms.

The whole volume is clear, conservative and should be very useful to medical students or to busy general practitioners who want some concrete suggestions as to how to handle their patients. Nowhere are there any attempts to explain psychotherapy, since this of course does not fall within the nurse's province, but for everything else we can recommend the book.

H. M.

The Parathyroids in Health and in Disease By DAVID H. SHILLING B.Sc., M.D. 335 pages, 17 X 25 cm, illustrated C. V. Mosby Company, St. Louis 1935 Price, \$5.00

This excellent book should prove quite valuable to special workers as well as to teachers and to those physicians and students who arrange for themselves the time to read authoritative monographs on special subjects.

The author is an acknowledged authority in the field of research on the parathyroids both experimental and clinical. His style is clear and concise. He has arranged the subject matter of the book into ten chapters dealing with the history, the anatomy, the pathology, the physiology of the parathyroids, the parathyroid hormone, tetany and hypoparathyroidism, hyperparathyroidism and osteitis fibrosa, the relation of the parathyroids to the other glands of internal secretion, the relation of the parathyroids to vitamin D, and the use and misuse of parathyroid hormone and of parathyroidectomy.

Numerous references in the text are made to the very full bibliography at the end of each chapter. It would seem to the reviewer that the world literature on the subject has been completely covered and listed.

The general excellence of the book is enhanced by the attractive format of the volume, of convenient size, excellent paper and print with many side headings in heavy black type.

T. P. S.

Cardiac Output and Arterial Hypertension By SIDNEY A. GLADSTONE, M.D. 56 pages, 16 × 23.5 cm 1935 Price, \$1.00

This small volume contains four papers, the first two dealing with the foreign gas methods of determining cardiac output, the third with the cardiac output in hypertension and the fourth presents an hypothesis concerning the mechanism of renal hypertension.

In the first two papers the author offers criticisms of the existing methods of determining cardiac output and presents his own modification of the acetylene method. In the third paper using his modification of the acetylene procedure, he presents evidence that the increased work of the heart in cases of essential hypertension is due to increased peripheral resistance and not to an increased cardiac output. The fourth paper is speculative in nature, and presents no experimental work of the author in support of his conclusions.

W. S. L., JR.

Roentgenographic Technique: A Manual for Physicians, Students and Technicians By DARMON ARTHEM RHINGGART, A.M., M.D., F.A.C.R., Professor of Roentgenology and Applied Anatomy, School of Medicine, University of Arkansas, Roentgenologist to St. Vincent's Infirmary, Baptist State Hospital, Missouri Pacific Hospital and the Arkansas Children's Hospital, Little Rock, Arkansas. Second Edition. 431 pages, 16 × 24 cm, 183 engravings. Lea and Febiger, Philadelphia. 1936. Price, \$5.50.

This is a thorough and successful attempt to present for physicians, students and technicians a text of time-tested roentgenographic technique as well as modern advances. Salient features of the volume are simplicity and comprehensiveness. The principles are presented in an orderly and logical fashion with emphasis on seemingly insignificant details of roentgenographic technique which make for thorough roentgenographic work. The sections on electricity and roentgen-ray machines and their accessories appear to be adequate to furnish the ground work for intelligent understanding of the principles.

A series of experiments is incorporated which should furnish invaluable information concerning operating characteristics of roentgen-ray machines, the laws of roentgen-ray exposure, and patient-tube-film relationship, so that the best films will be obtained. A technique based on thickness and radiographic density is advocated, a sound and universal method for obtaining consistently good roentgenograms. Sections on the radiographic peculiarities of the various parts of the body are included. The many methods of examining the various parts are mentioned, the best being more fully considered. The book should prove useful to any physician who desires a comprehensive knowledge of radiographic technique.

H. J. W.

Evaluation of Symptoms By OLIVER T. OSBORNE, M.D. 163 pages, 14 × 21 cm. Yale University Press, New Haven, Connecticut. 1935. Price \$3.50.

The author has written a small book in which he summarizes in seven chapters points which his long experience has shown him to be of particular value to the practicing physician. He discusses history taking, examination, principles of therapy, certain specific diseases and then takes up symptoms separately in alphabetic order. There is a great deal of information in small compass.

M. C. P.

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following gifts to the College Library of publications by members

- Dr Wm W Cadbury (Fellow) Moorestown N J on leave of absence
Canton China—1 autographed book, 'At the Point of a Lancet',
Dr Logan Clendinning (Fellow), Kansas City Mo—1 book 'The Balanced Diet',
Dr R Manning Clarke (Fellow) Los Angeles Calif—1 reprint,
Dr Albert Sorland (Fellow) Los Angeles Calif—2 reprints
Dr William E Costelow (Fellow), Los Angeles Calif—1 reprint,
Dr Isidore Lattman (Associate), Washington D C—3 reprints
Dr G Philip Gibbfield (Fellow), Boston Mass—18 reprints
Dr Samuel J McClendon (Fellow) San Diego Calif—2 reprints,
Dr Oliver I Osborne (Fellow) New Haven, Conn—1 reprint
Dr L B Caruthers (Associate), Miraj India—2 reprints,
Dr William C Cooke (Associate) San Diego, Calif—2 reprints,
Dr Warren W Quillian (Associate) Coral Gables, Fla—4 reprints,
Dr Joseph B Wolfe (Associate) Philadelphia Pa—2 reprints

THE WASHINGTON SCHOOL OF PSYCHIATRY

Early in 1933, the Training Committee of The Washington-Baltimore Psychoanalytic Society began a formal schedule of didactic lectures and seminars in keeping with the tradition of branch societies of The International Psychoanalytical Association. These training courses have been continued regularly from the beginning. The Committee incorporated the William Alanson White Psychoanalytic Foundation, and is now in view a psychoanalytic institute similar to that maintained in other training centers. However, experience of teaching and training dictated the need for graduate work in every field of interest to the psychiatrist. This led to plans for a school that would represent most truly American psychiatry and which would be limited in its scope. The outgrowth has been the incorporation of The Washington School of Psychiatry, with Dr White as its Honorary President. Among its officers in addition to Dr White, who is a Fellow of the American College of Physicians, are the following

- Dr Harry Stack Sullivan, President and Chairman of the Faculty
Dr Lucile Dooley, Vice-President
Dr Ross McClure Chapman (Fellow), Vice-President and Provost
Dr William K Ryan, Treasurer
Dr Ernest E Hadley (Associate), Secretary and Executive Director
Dr Joseph L Gilbert (Fellow), Registrar

STATE MEETING—ILLINOIS MEMBERS

The second annual meeting of the members of the American College of Physicians of the State of Illinois, outside of Chicago, was held September 24, 1936, at Peoria. The meeting was called by Dr Samuel E Munson, of Springfield, Governor for Southern Illinois, and the invitations were sent by Dr George Parker, of Peoria.

The meeting was held at the Creve Couer Club, and opened at four o'clock with the following guest speakers

- Dr Allen K Krause (Fellow) Baltimore, Md—"Future Possibilities of the Diagnosis of Tuberculosis",
 Dr Horace W Soper (Fellow), St Louis Mo—"Clinical Significance of Milk and Cholesterol in the Dietary of Man",
 Dr Frank Smithies (Master), Chicago, Ill—"Certain Ulcerative Lesions of the Bowel, Their Recognition and Management"

Dinner was served at six-thirty, after which a short report was made by Dr Samuel E Munson, Governor for Southern Illinois, who spoke in regard to the work of the committee that had been appointed about two years ago to act in connection with the Section on the Practice of Medicine of the American Medical Association to form an American Board for the purpose of establishing rules for the qualification of candidates and conducting examinations. This was accomplished in June of this year, with such rules and regulations as will govern its requirements for certification of those desiring to become internists. He also spoke of the officers of the College having acquired a suitable and permanent home for the College in Philadelphia. In addition to other requirements available, conference rooms may be used by members of the College as headquarters when in Philadelphia.

Dr Munson stated that inasmuch as the meeting at Springfield last year so unanimously met with approval, it was decided to accept the invitation of the Peoria Fellows and meet with them this year. It was agreed that no mistake was made in accepting this invitation, as we had ample proof of their cordiality and hospitality as good fellows upon this occasion.

When the call for this meeting reached the members through Dr George Parker, and the names of those who were to address the meeting were read, a thrill of pleasure and appreciation was felt that these distinguished Fellows were to be our guests and speakers. Not only were we honored by their presence as guests, but as clinicians and writers whose names are well known as authorities in their respective fields of medicine.

One of our guests whose name for many years has been synonymous with the most advanced thought in the diagnosis and treatment of tuberculosis, Editor of the *American Review of Tuberculosis*, was Dr Allen K Krause, of Baltimore.

Another whose name has been no less widely known as a teacher and author in the field of diseases of digestion was Dr Horace W Soper, of the Soper-Mills Clinic, St Louis.

Our third speaker, Secretary-General of the College from 1922 to 1926, and later its President, and the only one in Illinois who has been honored by being made a Master of the College, now Editor of the *American Journal of Digestive Diseases and Nutrition*, was Dr Frank Smithies, of Chicago.

In their letters of acceptance, each of these men expressed the appreciation and honor they felt in receiving an invitation to address the Fellows of the College from Illinois.

The following members of the College were present: Thomas A Starkey, of Beardstown, Gerald M Cline, Henry W Grote, Edgar M Stevenson, of Bloomington, D O N Lindberg, Perry J Mehuck, of Decatur, James C Redington, of Galesburg, Albert H Dollear, Warner H Newcomb, of Jacksonville, Orville Barbour, Harry A Durkin, Fred M Meixner, George Parker, Maxim Pollak, John R Vonachen, of Peoria, Warren F Pearce, Hildegard C Germann Sinnock, Harold Swanberg, of Quincy, Major Eugen G Remartz, of Chanute Field, Rantoul, Samuel E Munson, Thomas D Masters, Emmet F Pearson, George B Stericker, of Springfield, Villairs T Austin, Charles H Drenehahn, of Urbana.

There were also present about fifteen guests, invited by the Peoria Fellows, and Dr R L Green, of Peoria, President of the Illinois State Medical Society.

SPECIAL MEETING, BOARD OF REGENTS

A meeting of the Board of Regents of the American College of Physicians has been called by the President, Dr Ernest B Bradley at the College Headquarters in Philadelphia on December 13, 1936. Various committees of the College will meet December 12, as will also the American Board of Internal Medicine. About two hundred and fifty candidates for Associateship or Fellowship are to be considered and much other important College business will be transacted. The Committee on Constitution and By-Laws will present suggested amendments to the by-laws governing the admission of future candidates to Fellowship. The Committee on Future Policy for the Development of Internal Medicine may also present to the Regents recommendations for additional activities of the College in the future.

The New York Post-Graduate Medical School and Hospital conducted a Symposium on Dysentery September 26 1936. Among those presenting papers were Dr George W McCoy (Fellow), Director of the National Institute of Health Washington, D C, "Relationship of the Problem of Dysentery to the U S Public Health Service", Dr Ward J MacNeal (Fellow) Professor of Pathology and Bacteriology, New York Post-Graduate Medical School. "Bacteriophages in the Treatment of Intestinal Disease". Dr Z Bercovitz (Associate) Instructor in Medicine New York Post-Graduate Medical School, "Methods for Differential Diagnosis in Dysentery". Dr Walter G Lough (Fellow) Executive Officer, Department of Medicine, New York Post-Graduate Medical School acted as Chairman of that part of the program dealing with "Dysentery and the Clinician".

Dr D O N Lindberg (Fellow) Decatur, Ill, has been elected President of the Mississippi Valley Sanatorium Association.

Dr G Harlan Wells (Fellow) Philadelphia was elected President of the Homeopathic Medical Society of Pennsylvania on September 23, 1936. Dr E Roland Snader (Fellow), Philadelphia, was elected a trustee and Dr E W Stitzel (Fellow), Altoona, was elected censor.

Dr Frank S Horvath (Associate), Washington, D C, has been appointed Associate Professor of Clinical Medicine at Georgetown University School of Medicine.

Dr W D Weis (Fellow), County Health Commissioner for Lake County, Ind brought more forcibly to the residents of that County the matter of health and sanitation by having a Health and Sanitation Exhibit at the Lake County Fair during the past autumn. Exhibits and demonstrations were arranged under Dr Weis' direction by the Northwest Indiana Dental Society, the Lake County Tuberculosis Sanatorium, the Lake County Tuberculosis Association, the Weights and Measures Division of the Indiana Department of Public Health, the League for the Hard of Hearing, the Health Department of the City of Hammond, the Milk and Dairy Division of the Indiana Department of Public Health, the Lake County Safety Council, the Lake County Health Department and other agencies. Resort was made to motion pictures, charts, maps and various other means by which the interest of the citizens would be aroused and a proper impression of the importance of health measures carried to the homes throughout the County.

The Mississippi Valley Medical Society, being the Tri-State Post Graduate Assembly of Illinois, Missouri and Iowa, held its second annual meeting at Burlington Iowa, September 30 to October 2. Among the guest speakers was Dr Ralph Kinsella.

(Fellow), St Louis, Mo, representing Internal Medicine Dr Willard O Thompson (Fellow), Chicago, Ill, and Dr Leon Unger (Associate), Chicago, Ill, presented scientific exhibits on "Glands of Internal Secretion" and "Allergy," respectively. Among the clinical lecturers were Dr James G Carr (Fellow), Chicago, Ill, Dr Charles A Elliott (Fellow), Chicago, Ill, Dr F H Lamb (Associate), Davenport, Iowa, Dr Frank P McNamara (Fellow), Dubuque, Iowa, Dr Joseph L Miller (Fellow), Chicago, Ill, Dr Warren Pearce (Fellow), Quincy, Ill, Dr John H Peck (Fellow), Des Moines, Iowa, Dr J C Redington (Associate), Galesburg, Ill, Dr Howard Rusk (Fellow), St Louis, Mo, Dr Leon Unger (Associate), Chicago, Ill, and Dr Italo F Volini (Fellow), Chicago, Ill.

Among the officers of the Society were Dr D G Stine (Fellow), Columbia, Mo, First Vice-President, Dr J I Marker (Fellow), Davenport, Iowa, Third Vice-President, and Dr Harold Swanberg (Fellow), Quincy, Ill, Secretary-Treasurer Dr G M Cline (Fellow), Bloomington, Ill, Dr Harold Swanberg (Fellow), Quincy, Ill, and Dr E S Smith (Fellow), Kirksville, Mo, are members of the Board of Directors.

Dr Maximilian J Hubeny (Fellow), Chicago, has been made chief of the X-Ray Department of Cook County Hospital.

Dr George B Eusterman (Fellow), Rochester, Minn, Dr Alan Brown (Fellow), Toronto, Ont, and Dr Elliott P Joslin (Fellow), Boston, Mass, were among the guest speakers on the program of the Omaha Mid-West Clinical Society, held at Omaha, October 26 to 30.

Dr James J McGuire (Fellow), Trenton, has been elected Secretary of the New Jersey State Board of Medical Examiners.

Recent promotions on the Faculty of the College of Physicians and Surgeons of Columbia University include the following:

Dr J Burns Amberson, Jr (Fellow), Professor of Clinical Medicine
 Dr Robert L Levy (Fellow), Professor of Clinical Medicine
 Dr Alvan L Barach (Fellow), Assistant Professor of Clinical Medicine
 Dr Charles A McKendree (Fellow), Clinical Professor of Neurology

Dr Clarence M Grigsby (Fellow and former Governor for Texas), Professor of Clinical Medicine at Baylor University College of Medicine, Dallas, was guest of honor at a recent dinner celebrating his completion of twenty-five years as a member of the faculty of that institution.

Dr Ramon M Suarez (Fellow and Governor for Puerto Rico) addressed the first scientific meeting of the Puerto Rico chapter of the Pan American Medical Association in San Juan recently, on "The Study of the Bone Marrow in Chronic Schistosomiasis Mansonii."

Sir Frederick Banting (Fellow) and Dr Charles H Best, both of the University of Toronto Faculty of Medicine, and Dr James B Collip (Fellow), McGill University Faculty of Medicine, Montreal, were the recipients of the Frederick Newton Gisborne Starr Medal awarded at the last meeting of the Canadian Medical Association "for preeminent services to the cause of medicine in Canada." The Starr Medal was established in 1935 by the widow of the late Dr Starr, who for several years was the General Secretary of the Association, and President in 1927.

Among the guest speakers at the annual meeting of the Indiana State Medical Association at South Bend, October 6 to 8, were the following Fellows of the College

Dr Byrl R Kirklin, Rochester, Minn
Dr Russell L Cecil, New York City
Dr Francis E Senear, Chicago, Ill
Dr Elmer L Sevringhaus, Madison, Wis
Dr John A Ioomer, Cleveland, Ohio

Dr Hugo A Freund (Fellow), Detroit, President of the Children's Fund of Michigan, presented a symposium on "What Constitutes a Complete Health Service for the Community?" at a conference between the University of Michigan and the Fund, at Marquette, recently Dr Arthur C Curtis (Fellow), Ann Arbor, delivered an address on "Etiology and Management of Chronic Arthritis"

The following Fellows of the American College of Physicians addressed the Fourteenth Annual Conference of the Kansas City Southwest Clinical Society at Kansas City, October 4 to 8

Dr Milton A Bridges, New York City
Dr Joseph A Capps, Chicago, Ill
Dr J Arthur Myers, Minneapolis, Minn

Dr Morris Maslon (Fellow), Glens Falls, N Y, was a guest of honor at a testimonial dinner at the Fort William Henry Hotel, Lake George, recently, celebrating his twenty-fifth anniversary as head of the Warren County Laboratory

Dr Coy C Carpenter (Fellow), who has been acting dean of Wake Forest College of Medicine, Wake Forest, N C, has now been elected dean to succeed Dr Thurman D Kitchin (Fellow), who was made president of the College in 1930

Dr Edward S King (Associate), Professor of Physiologic Chemistry and Bacteriology, is on leave of absence, spending the present term at Harvard University Medical School, Boston

The first "Harlow Brooks Memorial Navajo Clinical Conference" was held August 31 to September 1 at Ganado, Ariz Among the speakers was Dr Milo K Tedstrom (Fellow) of Santa Ana, Calif The conference will be held annually and is named in honor of the late Dr Harlow Brooks (Fellow), New York City, who was interested in the work of the Sage Memorial Hospital at Ganado, which is in the heart of the Navajo reservation Dr Brooks was an authority on Indian practices and customs

The Iowa State Medical Society has been offering graduate courses in various Iowa cities during the present autumn Dr Arthur U Desjardins (Fellow), Rochester, Minn, gave a lecture on "Evaluation of Radiologic Diagnosis and Treatment of Cancer", Dr Samuel A Levine (Fellow), Boston, "Modern Cardiac Therapy", Dr William S Middleton (Fellow), Madison, Wis, "The Barbiturates in the Treatment of Disease", Dr Paul A O'Leary (Fellow), Rochester, Minn, "Treatment of Syphilis", Dr Philip S Hensch (Fellow), Rochester, Minn, "Diagnosis and Treatment of Arthritis", Dr Maurice C Howard (Fellow), Omaha,

Nebr, "Diagnosis and Treatment of the Anemias", Dr Byrl R Kirklin (Fellow), Rochester, Minn, "Roentgenologic Diagnosis", and Dr Russell M Wilder (Fellow), Rochester, Minn, "Modern Treatment of Diabetes"

Dr John Harvey (Fellow), Lexington, Ky, delivered the annual oration in medicine of the Kentucky State Medical Association at Paducah on October 6, his subject being "Our Duty to the Art and Science of Medicine"

Dr George Herrmann (Fellow), Galveston, Tex, addressed the seventy-first annual meeting of the Michigan State Medical Society, September 21 to 24, on "Further Studies of the Mechanism of Action and of the Relative Effectiveness of the Newer Diuretics"

The Ohio State Medical Association held its ninetieth annual meeting in Cleveland, October 7 to 9, under the presidency of Dr Ralph R Hendershott (Associate), Tiffin, Ohio

Dr Samuel A Levine (Fellow), Boston, assistant professor of medicine, Harvard University Medical School, delivered a lecture on "Diseases of the Heart and Allied Pathologic Conditions" in connection with the graduate lectures sponsored by the Lima and Allen County (Ohio) Academy of Medicine during September

The Medical Society of Milwaukee County, Wisconsin, sponsored a course of graduate lectures on syphilis given at Marquette University School of Medicine, Milwaukee, recently. Among the lecturers and their subjects were

Dr Udo J Wile (Fellow), Ann Arbor, Mich, 'Bone, Joint and Visceral Syphilis", Dr James E Paulin (Fellow), Atlanta, Ga, "Public Health Aspects of Syphilis", and Dr Paul A O'Leary (Fellow), Rochester, Minn, "Treatment of Syphilis"

Col Henry C Pillsbury (Fellow), Medical Corps, U S Army, has been assigned to duty as chief health officer of the Panama Canal Zone

Dr Frank H Krusen (Associate), Rochester, Minn, and Dr William J Egan (Fellow), Milwaukee, Wis, have been elected vice-presidents of the American Congress of Physical Therapy for the coming year

Dr Ernest B Bradley (Fellow and President) addressed the Jefferson and Fayette County Medical Societies at Louisville, Ky, September 21, on "A Medical Glance at the Past Thirty Years"

Dr George W McCoy (Fellow), Director of the National Institute of Health, Washington, D C, was one of the speakers on the occasion of the dedication of the new public health laboratory of the New York City Department of Health, named in honor of Dr William Hallock Park, founder and director emeritus of the laboratory

Dr William S McCann (Fellow), Rochester, N Y, and Dr Elliott P Joslin (Fellow), Boston Mass, were guest speakers at the eighty-sixth annual meeting of the Medical Society of the State of Pennsylvania, held in Pittsburgh October 5 to 8

Dr Kenneth M Lynch (Fellow) and Dr Joseph H Cannon (Fellow), both of Charleston, S C, and Dr James E Paullin (Fellow), Atlanta, Ga, delivered lectures on diseases of the kidney at the second annual clinical assembly presented by the Anderson County (South Carolina) Medical Society, September 8 to 10

Dr Edgar A Hines (Fellow), Seneca S C, was president of the assembly

Dr John A Kolmer (Fellow), Philadelphia, and Dr Josephine B Neal (Fellow), New York City conducted a panel discussion on poliomyelitis in connection with the fourth annual fall clinical session of the Maine Medical Association, held at Waterville, Maine, October 15 to 16

Dr Paul Dudley White (Fellow) assistant professor of medicine, Harvard Medical School, delivered the principal address on the occasion of Ether Day at the Massachusetts General Hospital, October 16

The New York Academy of Medicine presented its ninth annual graduate fortnight October 19 to 31, on "Trauma Occupational Diseases and Hazards" Among the speakers and their subjects were

Major Samuel A White (Fellow), Medical Corps, U S Army "Medical Aspects of Chemical Warfare", Dr Elliott P Joslin (Fellow), Boston, "Relation of Trauma to Diabetes", and Dr J Burns Amberson, Jr (Fellow), New York City, "Pulmonary Disease"

The late Dr James M Anders (Master), Philadelphia, who died August 29, provided in his will after the death of his widow \$50,000 for the establishment of the James M Anders Foundation in the Graduate School of Medicine of the University of Pennsylvania, \$2,500 to the Philadelphia County Medical Society to defray the expenses of the annual "Public Health Day" in the public schools, \$2,000 for the endowment fund of the Society's library, and further provided that the library committee of the Philadelphia County Medical Society may select such books from his library as they choose

Dr Julius H Hess (Fellow), Chicago, and Dr John A Toomey (Fellow), Cleveland, will be guest speakers at the fourth annual meeting in Atlanta of the Georgia Pediatric Society, December 10

Dr Wyndham B Blanton (Fellow), professor of the history of medicine, Medical College of Virginia, has been appointed one of the editors of the "Annals of Medical History"

The seventh annual fall clinical conference of the Oklahoma City Clinical Society was held October 26 to 29 Among the speakers and their titles were the following

Dr Wilburt C Davison (Fellow), Dean of the School of Medicine and Professor of Pediatrics, Duke University, Durham, N C—Pediatrics,
 Dr Charles L Brown (Fellow), Professor of Medicine and Head of the Department of Medicine, Temple University School of Medicine, Philadelphia—Internal Medicine,

Dr F E Senear (Fellow), Professor and Head of the Department of Dermatology, University of Illinois College of Medicine, Chicago—Dermatology,
Dr Hans Lissner (Fellow), Clinical Professor of Medicine, University of California Medical School, Berkeley-San Francisco—Endocrinology

Dr F O Mahony (Fellow), El Dorado, Ark, has been appointed vice-president of the State Board of Health

Dr Paul Brindley (Fellow), Galveston, and Dr May Owen (Fellow), Fort Worth, have been elected president and vice-president respectively of the Texas State Pathological Society

Dr Alex F Robertson, Jr (Fellow), Staunton, Va, has been elected secretary of the Augusta County (Virginia) Medical Society

Honoring the sixty-seventh birthday of Dr Francis M Pottenger (Fellow and ex-President), a large number of patients and former patients joined members of Dr Pottenger's family and the Staff of the Sanatorium in an informal reception given for him on Sunday afternoon, September 27, in the beautiful gardens of the Pottenger Sanatorium at Monrovia, Calif. There were about two hundred guests present, among whom were patients who left the Sanatorium as far back as 1905

Dr Pottenger received many beautiful gifts from associates and patients, and congratulatory telegrams from patients and friends unable to attend. A buffet supper was served in the gardens

Major James Stevens Simmons (Fellow), Medical Corps, U S Army, who in 1934 organized the Army Medical Research Board, Ancon, Canal Zone, and who during the past two years has been engaged in an investigation of malaria and its anopheline vectors in Panama, has been transferred for duty as Assistant to the Corps Area Surgeon, Headquarters First Corps Area, Army Base, Boston, Mass

Dr Chester North Frazier (Fellow), Professor of Dermatology and Syphilology, Peiping Union Medical College, Peiping, China, is on furlough and is engaged in studying biostatistics in the School of Hygiene and Public Health of the Johns Hopkins University, Baltimore

Dr Paul P McCain (Fellow), Medical Director of the North Carolina Sanatorium for the Treatment of Tuberculosis, has been awarded the degree of LL D by the University of North Carolina

Dr Perry J Melnick (Associate), Decatur, Ill, received the degree of Doctor of Philosophy in Pathology from the University of Illinois College of Medicine last June

Dr Allen K Krause (Fellow), Director of the Desert Sanatorium, Tucson, Ariz, is on leave of absence and is now in Baltimore, Md, where he was formerly Associate Professor of Medicine on the faculty of Johns Hopkins University. Dr Krause still retains the title of Lecturer in Medicine at Johns Hopkins University School of Medicine, and is a "Fellow by Courtesy in Epidemiology" in the Johns Hopkins School of Hygiene. He is Editor of the "American Review of Tuberculosis," and during the coming year will devote his time to study and writing

OBITUARIES

DR WILLIAM H MAYER

In the death of Dr William H Mayer (Fellow) on August 22, 1936, from septic pneumonia, organized medicine lost one of its most loyal supporters, one who in spite of almost unsupportable physical handicap had been unsparing of time and energy in his devotion to the affairs of his county and state societies and of the American Medical Association

Dr Mayer was born in Pittsburgh, Pa, October 30, 1887, the son of William L and Anna Bickman Mayer

He received his preliminary education in Pittsburgh Central High School, and after graduating from the University of Pennsylvania Medical School in 1912, served his internship in Mercy Hospital, Pittsburgh. Entering into practice he devoted himself to the field of neurology and psychiatry. Dr Mayer was Neurologist to Allegheny General Hospital and Passavant Hospital, Associate Psychiatrist to St Francis Hospital, Assistant Professor of Neurology in the School of Medicine of the University of Pittsburgh. In addition to membership in the County and State societies he was a Fellow of the American Medical Association, the Pittsburgh Academy of Medicine and the American College of Physicians. He was a member, also, of the American Psychiatric Association and of the Association for Research in Mental and Nervous Diseases.

Dr Mayer served as secretary of the Allegheny County Medical Society from 1917 to 1925, in which year he became President-Elect of the Medical Society of the State of Pennsylvania.

He also served his county society, as a member of the Board of Directors, chairman of the Finance Committee, and as elected delegate to the State Society. In 1931 he was installed as President of the Medical Society of the State of Pennsylvania. Consecutively, since 1921 he was chosen to succeed himself as delegate from his State Society to the House of Delegates of the American Medical Association.

Dr Mayer was twice married, his first wife was Miss Emma J Glass of London, Ontario, who died several years ago. He later married Miss Virginia Diehl Sutton of Pittsburgh, who with their baby daughter, Ann Virginia, born February 29, 1936, survives him.

E BOSWORTH MCCREADY, M D, F A C P,
Governor for Western Pennsylvania

DR HOWARD E MARCHBANKS

Dr Howard E Marchbanks (Fellow), of Pittsburg, Kansas, died August 7, 1936, of coronary occlusion.

Dr Marchbanks was born in Scammon, Kansas, July 18, 1888. He graduated from Cherokee High School, entered the University of Kansas

and received his A B He then entered the University of Kansas Medical School and graduated in 1916 He served his internship at the Bell Memorial Hospital in Kansas City, Kansas

He was a member of the Phi Beta Pi Medical Fraternity During the World War he served as First Lieutenant in the Medical Corps attached to the 218th Engineers He received his discharge from the service February 4, 1919

In 1919 Dr Marchbanks took postgraduate work under Dr Richard Cabot in the Harvard Medical School at Boston He was a member of the American Medical Association, The Kansas Medical Society, The Southeast Kansas Medical Society, The Jackson County (Missouri) Medical Society He was one of the associate editors of the Journal of the Kansas Medical Society In 1931 Dr Marchbanks was made a Fellow of the American College of Physicians

THOMAS T HOLT, M D , F A C P ,
Governor for Kansas

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THE MANNER IN WHICH FOOD CONTROLS THE BULK OF THE FECES

By RAY D. WILLIAMS, M.S., and W. H. OLMSFED, M.D.,
St. Louis, Missouri

EVERYONE is fully aware that the causes of constipation are numerous. It is often very difficult to determine the relative importance of each factor. There are many normal people who, although consuming very concentrated, highly purified, non residue diets, are nevertheless rarely constipated. Others there are who in spite of using all possible dietary aids are not able to have a daily evacuation of the bowels. So there is considerable doubt in our minds as to whether food is the main factor in determining the regularity of stool evacuation. Furthermore, there is abundant room for argument as to whether or not a daily evacuation is necessary for the maintenance of sound health.

One need not be concerned with the causes or clinical import of constipation to be able to prove that in a given normal individual one can markedly affect the stool volume by dietary means.

In this paper we wish to present the experimental results accumulated from time to time over the past several years by using as experimental subjects medical students who trained themselves to a regular time for stool evacuation. It is our conviction that results in this field are much more convincing and applicable if the human subject is used as the experimental animal. With these normal individuals we propose to show the effects of food on the volume of the stool. We shall then explain partially at least the results found.

EFFECTS OF DIGESTIBLE PROTEIN, FAT AND CARBOHYDRATE

Both clinicians and physiologists agree that the indigestible carbohydrates of foods have a greater effect on stool volume than the digestible and absorbable protein, fat and carbohydrate. Nevertheless, one can easily

* Presented at the Detroit meeting of the American College of Physicians, March 2, 1936.
From the Department of Medicine, Washington University School of Medicine, and the Barnes Hospital, St. Louis, Missouri.

show the effect of carbohydrate even in the case of non residue diets on the volume of the stool. In table 1 are recorded the results of an experiment carried out in 1929¹ on three students. It can be seen that when there was a predominance of carbohydrate in the diet, the stool volumes exceeded those found in the periods of either high protein or high fat feeding. When much protein was fed, the small stool volume is very evident. Although all three subjects' stool volumes increased on high carbohydrate diets, there are differences in the individual responses. This illustrates the difference found among normal individuals.

The explanation of the different effects of protein, fat and carbohydrate on the stool volume lies in the fact that even in case of non residue diets

TABLE I
Influence of Digestible Protein, Fat and Carbohydrate on the Volume of the Stool

Diet 7-day Periods	Protein	Fat	Starch	Sugar	Average 24-hr Volume of Stool		
					Subjects		
					K	McC	M
	gm	gm	gm	gm	gm	gm	gm
High protein	250	70-100	55-70	30-40	83	55	180
High sugar	50	100	135	365	222	205	329
High starch	50	100	400	100	193	121	253
High fat	50	300	75	25	126	118	211

which are from 90 to 95 per cent digested and absorbed, there is, nevertheless, a residue which reaches the bacteria-infested large intestine. The diet determines the character of this residue. That even small amounts of sucrose reach the colon is probable because of its relatively slower absorption rate² as compared to glucose and galactose. The putrefactive products of protein are probably, taken as a whole, costive in their effects. On the other hand the products of carbohydrate fermentation are the lower volatile fatty acids, lactic acid and carbon dioxide, which are definitely proved to be laxative³. Furthermore, it must be remembered, as emphasized by Kendall,¹ that bacteria will break down sugar in preference to protein for their energy needs. Thus, in the intestine just as in culture media, as long as food residues contain a certain amount of sugar, protein breakdown (putrefaction) is spared, i.e., reduced to a minimum. Thus a high carbohydrate diet has at least two effects:

(a) The products of sugar fermentation are laxative.

(b) The presence of sugar spares the breakdown of protein and thus minimizes the formation of costive products of putrefaction.

Table 2 shows that the volatile fatty acids in stools of normal men are increased by high carbohydrate diets and that the amounts of volatile fatty acids increase with the rise in stool volume. Pediatricians⁵ have long recognized the laxative nature of these acids and that their increased output accompanies sugar feedings to infants.

Lactic acid appears in cultures of almost all types of bacteria as long as there is abundance of sugar in the media. Pittman and Ohnsted⁶ could not demonstrate lactic acid in human stools. We interpret this finding as evidence of the remarkable symbiotic action of the many types of bacteria found in the intestine. Lactic acid incubated in raw fecal matter disappears.

Carbon dioxide and hydrogen are produced in largest quantities when sugar predominates in the diet. Physicians should realize that these gases are normal excretory products of bacterial fermentation. Many people and some physicians look upon the passage of flatus as an abnormal condition, whereas it is as normal as the passage of feces.

TABLE II
Effect of Diet (Non-Residue) on Total Volatile Fatty Acid Excretion

Diet	Average c c 0.1 N acid in 24 hours		
	Subjects		
	K	McC	M
High protein	c c 90	c c 71	c c 179
High sugar	148	278	447
High starch	125	191	349
High fat	82	129	221

THE INDIGESTIBLE CARBOHYDRATES

When the physician is called upon to prescribe a diet as an adjunct in the treatment of constipation, he instructs his patient to take a "bulky" diet. He means by this that the diet should be rich in vegetables, fruits, and the bran of cereals. These foods contain indigestible carbohydrates which are supposed to pass through the upper intestinal tract unchanged and thus add to the bulk of the feces. The present conception of the action of bulky foods can be expressed by a quotation from Starling's "Textbook of Physiology"⁷ (p. 597): "The indigestible cellulose in the food is not without value. It has been shown previously that the peristaltic contractions of the intestine are roused primarily by the mechanical stimulus of distention. If the food is capable of entire digestion and absorption, the amount of feces formed is limited to that produced by the intestinal wall itself. The small bulk exercises very little stimulating effect on the intestine, and the

movements of the latter will therefore tend to be sluggish, especially in the absence of the mechanical stimulus determined by physical exercise. The presence of a certain amount of cellulose in the diet may therefore be of considerable advantage by giving bulk to the feces and ensuring the proper regular evacuation of the lower gut. It is probable that the constipation which is so common a disorder in civilized communities is due as much to the refinement in the preparation of food as to the prevalence of sedentary occupations incident on the working of such communities." The current belief, therefore, emphasizes the mechanical distention of the colon by bulky foods as the stimulus which prompts evacuation. The results of the experiments we are about to show suggest another important factor in addition to the mechanical one.

The indigestible portion of carbohydrate foods consists of the structural material of plants. Chemically it can be divided into three groups: cellulose, lignin, and hemicellulose. Cellulose is a polysaccharide which can be converted into glucose. It is insoluble in water, cannot be broken up by any of the enzymes of the mammalian intestinal tract, but can be broken down to glucose by the hydrolytic action of concentrated mineral acids. Lignin is an incrustation associated closely with cellulose and found in the harder portions of the structural parts of plants, especially in wood. The cellulose-lignin combination is dissociated by chlorine, sulphite solutions, strong alkalis and mineral acids. Lignin is not a carbohydrate. The hemicelluloses are a group of polysaccharides, soluble in dilute alkalis and for the greater part convertible into simple sugars by dilute acid hydrolysis. The sugars making up the major portion of various hemicelluloses are the pentoses (five carbon sugars), galactose, levulose and mannose. Although neither lignin, cellulose nor hemicellulose can be digested, nevertheless they all can be attacked by bacteria. If this were not so, our farm animals grazing on pastures would have great difficulty in maintaining their nutrition. In the intestinal tracts of herbivora bacteria convert cellulose and the hemicelluloses to much the same products as they do in the case of the soluble sugars and starches. It has been estimated that the grazing animal obtains as much as 25 per cent of his calories from the absorption of the fatty acids which bacteria produce by the fermentation of cellulose and hemicelluloses. Pringsheim⁸ has discussed this matter fully. These well known facts raise several very pertinent questions. Are cellulose and hemicelluloses broken down in the same fashion in the intestinal tract of man, and, if so, is the action of bulky foods mechanical or chemical? If bacteria do break down cellulose and hemicellulose to soluble products, how can their effect be a mechanical one? To what extent are cellulose, lignin and hemicelluloses broken down by bacteria in the intestinal tract of man? The literature does not contain satisfactory answers to these questions,⁹ because of the absence of satisfactory methods for determining quantitatively cellulose, lignin and the hemicelluloses.

If one studies an analysis of any cereal food product, he finds listed protein, fat, starch, ash, moisture and crude fiber. Crude fiber is the term used by analytical food chemists to denote the indigestible fraction of foods. The method for determining crude fiber goes back seventy years. It originated in the little town of Weende, Germany, and is known also as the Weende method. This procedure makes use of a double digestion, first with weak acid and second with weak alkali. Between each digestion the soluble products are filtered off and discarded. The crude fiber is what remains after these digestions. Chemists have long known that crude fiber represented merely an unknown fraction, varying with each material analyzed, of the combined cellulose, lignin and hemicellulose. Because the crude fiber method was completely unsatisfactory as a means of studying the amounts of indigestible residue in foods and feces, Williams and Olmsted¹⁰ published a biochemical method for the quantitative determination of each constituent of indigestible residue. It gave us the opportunity of conducting an experiment to determine the true action of bulky foods.

This experiment¹¹ was conducted with medical students. The materials fed were indigestible residues isolated from widely varying sources, concentrated by simple means which carefully preserved their essential chemical composition. Table 3 shows that 50 to 80 per cent of these

TABLE III
Analysis of Materials Fed

Materials added to basal diet	Wheat bran	Alfalfa leaf meal	Carrots	Corn germ meal	Cotton seed hull meal	Sugar beet pulp	Canned peas	Cabbage	Agar agar	Cellu flour
	%	%	%	%	%	%	%	%	%	%
Cellulose	16.9	32.5	23.2	15.8	19.4	34.2	35.0	29.5	0.0	78.8
Lignin	7.8	15.0	3.4	2.4	20.8	2.5	1.7	2.6	0.0	0.0
Hemicellulose	35.2	19.2	28.8	30.8	31.5	29.2	10.9	28.3	81.0	16.9
Starch, protein, ash, moisture and fat	35.7	32.7	40.6	49.7	17.5	30.3	49.5	37.1	8.5	3.1
Total	95.6	99.4	96.0	98.7	99.2	96.2	97.1	97.5	99.5	98.8

residues consisted of cellulose, lignin and hemicellulose, but that no two of these residues had the same composition. This affords opportunity for studying the relative effects of cellulose, hemicellulose and lignin. Before our experiment we did not know which of these three components was most important. We, therefore, maintained the amount of cellulose plus lignin constant (10 gm per day) and let the amount of hemicellulose be variable. To a basal diet of non-residue foods each residue was added for a period of six days. The stools were analyzed for volatile fatty acids, cellulose, lignin, hemicellulose and reducing sugars.

CRITERIA OF LAXATIVE ACTION

Obviously a material is not laxative merely because it increases the stool weight. If this were not so, inert materials recoverable 100 per cent in the feces would be considered laxative. We have found that certain materials of vegetable origin classed as roughage are almost completely recovered in the stools, do add to the weight of a basal stool but are quite constipating whether judged subjectively or by trauma to the colon. We adopted two criteria: (1) The impression of the subject as to whether or not the bowel movement was satisfactory. (2) The weight of feces over and above the weight of the residue recovered in the feces. For instance, if 70 gm of substance *A* were fed, 65 gm recovered in the feces and the weight of feces increased only 90 gm, this material could not be considered laxative. If, on the other hand, 100 gm substance *B* were fed, 29 gm recovered in the feces and the weight of feces increased 550 gm, this substance would be considered laxative.

As an index of true increase in stool weight we adopted a factor, termed "Increment in Stool Weight," which is obtained by subtracting from the stool weight of a residue feeding period the weight of residue passing the gut and the weight of a basal (residue free) period stool. This increment represents either increased free fluid content or water absorbed by the residue remaining in the stool.

RESULTS

Table 4 shows the increment in stool weights for seven days after these residues had been fed for six days. Basal stool weights were markedly increased in the cases of bran, carrots, corn germ meal, cabbage, agar and sugar beet pulp. Poor subjective results with only slight increment in stool

TABLE IV
Relative Effectiveness of Materials Fed

Materials Added to Basal Diet	Weight of Residue Fed	Increment in Stool Weight				Ratio Increment to Residue Fed
		Subject F	Subject W	Subject H	Average of F, W and H	
	gm	gm	gm	gm	gm	
Cellu flour	71.7	223	119	(-) 63	93	1.34
Cotton seed hull	105.9	104	123	66	97	0.91
Canned peas	74.5	114	255	134	167	2.24
Alfalfa leaf	79.5	182	318	221	240	3.04
Sugar beet pulp	93.4	662	372	171	401	4.29
Wheat bran	146.0	575	578	373	475	3.25
Carrots	106.8	700	589	336	541	5.06
Corn germ meal	154.4	590	563	581	578	3.74
Cabbage	101.5	647	781	449	625	6.15
Agar agar	80.2	835	719	445	666	8.30

weights are noted in the cases of cellu flour, peas, cotton seed hull and alfalfa leaf. These results take on significance when we compare the relative increases in stool weights with the chemical analyses of the residues. Table 3 shows these analyses. The cellulose varies in most of the materials between zero and 35 per cent, lignin between zero and 21 per cent, and hemicellulose between 10 and 35 per cent. In table 5 the characteristics of the chemical composition are stated very simply. Each material, which when fed resulted in a substantial increment of stool weight (essentially doubling of basal stool weight), is boxed.

TABLE V

Classification of Residues on the Bases of the Increase of Stool Volume and Their Chemical Composition

<u>High in cellulose</u>	{ Alfalfa leaf, beet pulp , peas cabbage and cellu
<u>High in lignin</u>	{ Alfalfa leaf, cotton seed hull
<u>High in hemicellulose</u>	{ Bran , carrots , corn germ meal , Cotton seed hull, beet pulp , Cabbage agar

A glance leaves not much doubt that when hemicellulose is high, the residue is apt to be laxative. Seven of these 10 materials fed proved on analysis to contain 30 per cent or more hemicellulose. Of these seven, six, when fed, resulted in a marked increment of stool weight.

Two materials contained 15 to 20 per cent lignin, the remaining materials contained only 1 to 3 per cent lignin. Alfalfa leaf and cotton seed hull, when fed, resulted in stool weights very little above the basal level.

Five of these residues were high in cellulose. That is, the analyses showed at least 30 per cent cellulose. Of these five, only two (cabbage and sugar beet pulp) resulted in marked increment of stool weight. Cellu flour was 79 per cent cellulose and when it was fed, the stools were of low weight. If cellulose were stimulating because of its mechanical bulk, one would expect cellu flour to be highly stimulating, but such is not the case.

From this analysis, we conclude that the comparison of these materials shows that when hemicelluloses predominate in the residue, the stool weights increase definitely, when lignin is present, in percentages as high as 20, the stools are increased above the basal level only to the extent of the material fed. Cotton seed hull was over 30 per cent hemicellulose. This level in other materials resulted in marked increase of stool weight but the 20 per

cent lignin present in cotton seed hulls apparently counteracted the effect of hemicelluloses. The explanation will be considered below.

DISAPPEARANCE OF INDIGESTIBLE RESIDUES

The analysis of the stools for lignin, cellulose and hemicellulose revealed a remarkably high percentage of disappearance of these substances during their passage through the human gut. Table 6 summarizes the disappear-

TABLE VI
Disappearance of Lignin, Cellulose and Hemicellulose

Residue Added to Basal Diet	Fractions of Indigestible Residue						Total Residue	
	Lignin		Cellulose		Hemicellulose			
	gm	%	gm	%	gm	%	gm	%
Wheat bran	1.9	10	11.4	30	29.8	35	43.1	30
Corn germ meal	*	*	29.5	57	59.5	63	89.0	60
Carrots	*	*	34.5	67	39.5	85	74.4	74
Cotton seed hull	3.7	12	4.8	14	10.6	30	19.1	18
Cabbage	*	*	29.8	55	33.1	80	62.9	80
Sugar beet pulp	*	*	30.9	55	29.7	89	60.6	65
Alfalfa leaf meal	0.6	3	5.0	12	1.1	6	6.7	9
Canned peas	*	*	25.4	45	12.1	84	37.5	53
Agar agar	—	—	—	—	48.6	60	48.6	60
Cellu flour	—	—	4.2	7	3.2	29	7.4	10

* Lignin content too small for valid results

ance of each material fed. Lignin was present in bran, cotton seed hull and alfalfa leaf in a considerable quantity. The stools passed during the feeding of these substances contained 88 to 97 per cent of the amounts fed. The lignin present in the other substances fed was so small that the high percentage disappearance, in our opinion, is of no significance. Lignin then is very resistant to bacterial attack. Cellulose disappeared to the extent of 7 per cent in the case of cellu flour, up to 67 per cent in the case of carrots. In six of the materials fed more than 45 per cent of the cellulose was lost during its passage through the intestinal tract. Apparently bacteria have little difficulty in attacking the hemicelluloses for they disappeared to a greater extent than either lignin or cellulose. In six of the 10 materials fed the total loss in this fraction was over 60 per cent. In the case of carrots, cabbage, beet pulp and peas over 80 per cent of the hemicellulose was lost. The summary of the total losses of indigestible residue show that in six of the 10 materials fed from 53 to 74 per cent disappeared as they passed through the intestinal tract.

The three materials resistant to bacteria (bran, cotton seed hull, and alfalfa leaf) contained considerable amounts of lignin. That foodstuffs high in lignin are resistant to bacterial degradation in the intestinal tracts of

farm animals is well known. In Germany during the war the delignification of straw was studied, and it was found that the treatment of straw with alkali, which broke up the association of lignin and cellulose, resulted in a material much more nourishing to herbivorous animals (see Pringsheim). In our experiments lignin was not broken down when present in considerable quantity and, furthermore, its presence prevented the breakdown of both cellulose and hemicellulose. It has been previously pointed out that no increase in volume of stools occurred after the feeding of the two materials highest in lignin, i.e., cotton seed hull and alfalfa leaf.

Cellu flour is a material produced (according to the manufacturer) by "hydrolyzing bleached fiber." In other words, it has been prepared in much the same way as crude fiber by the action of acid and alkali. We believe that this strong chemical treatment removes the portion of cellulose and hemicellulose which bacteria are able to attack and thus leaves it inert.

MECHANISM OF LAXATIVE ACTION OF INDIGESTIBLE RESIDUES

Since hemicellulose to a great extent and cellulose to a lesser degree disappear in passing through the human intestinal tract, they must be attacked by bacteria and if this be so, the metabolic products should be demonstrable. The products of carbohydrate residue breakdown are methane, carbon dioxide, hydrogen, alcohols and volatile fatty acids. Volatile fatty acids are easily determinable end products and are good indices of residue breakdown provided the soluble carbohydrate portion of the diet is regulated. Since these acids arise from the degradation of hemicellulose and cellulose, there should be a parallelism between the percentage of disappearance of those latter substances and the volume of volatile fatty acids recovered from the feces. Moreover since volatile fatty acids arising from any source (i.e. soluble or insoluble carbohydrates) are laxative, there should be a parallelism between the percentage disappearance of cellulose and hemicellulose, the stool content of volatile acids and the increment of stool weight. Table 7 shows this to be the case. The values are averages of three human subjects. The output of volatile acids formed after feeding those residues which were laxative exceeded those formed on high sugar diets.

In table 7 attention is called to the results in the case of agar agar. It was the most effectual of all materials fed in increasing the volumes of the stools. This substance is 81 per cent hemicellulose and therefore in comparison with the other types of indigestible materials fed, there should have been a greater percentage of the agar broken down and greater production of volatile fatty acids. That this was not so suggests that the effectiveness of agar is due to some other property which the other materials studied did not possess or possessed to a much less degree. The striking characteristic of agar is its ability to take up and hold water. It is this property which makes it such a fine foundation for culture media. The action of mineral cathartics is due to their ability to prevent the absorption of water by the

colonic epithelium Any food residue that is highly hygroscopic keeps the feces pliable and plastic and makes for their easy evacuation by peristaltic rushes If this explanation is correct, the hygroscopic property of the portion of food residues escaping bacterial degradation is of some importance and assists fecal evacuation The effectiveness of agar is by no means wholly due to its hygroscopic property Sixty per cent of the agar was broken down and the volume of fatty acids produced corresponded well with the amount of agar disappearing

In brief, an effective residue is one which is free from lignin, contains a preponderance of hemicellulose, is finely divided so that bacteria may break it down into laxative products and which after bacterial action yields a remainder with water binding properties ensuring a bulky, plastic, easily evacuated stool

TABLE VII
Relation of Increment in Stool Weight to Disappearance of Residue
and Recovery of Volatile Fatty Acids

Materials Added to Basal Diet	Increment in Stool Wt	Cellulose plus Hemicell Disappearing	Increment Volatile Fatty Acids (0.1 N Alk.)	Ratio Increment Stool Wt to Wt Residue in Stool	Subjective Estimation of Laxative Value (1 Least)
	gm	gm	c c		
Cellu flour	93	7.4	35	1.45	2
Cotton seed hull	97	15.4	282	1.13	3
Canned peas	167	37.5	448	4.77	4
Alfalfa leaf	240	6.1	278	3.00	1
Sugar beet pulp	401	60.6	980	12.30	7
Wheat bran	475	41.2	1013	4.65	5
Carrots	541	74.4	970	19.30	9
Corn germ meal	578	89.0	1002	9.34	8
Cabbage	625	62.9	1352	17.90	10
Agar agar	666	48.6	896	20.80	6

SUMMARY

These researches into the physiology of bulky foods as represented by the 10 substances studied have led us to the following conclusions

Of the three classes of substances which make up the effective portion of indigestible residues, the hemicelluloses are the most efficacious in increasing the bulk of the stool Cellulose in its natural state is not as effective as the hemicelluloses (We suspect that highly hygroscopic residues may be very effective) Residues high in lignin are costive

Contrary to the accepted belief, the effectiveness of indigestible residues is not due primarily to the mechanical stimulus of distention but rather to chemical stimuli which arise from the destruction of hemicelluloses and cellulose by the intestinal bacterial flora One of these stimulating products is the lower volatile fatty acids There may be others

The chemical stimuli are aided by the hygroscopic quality of the residue escaping degradation. There may be other types of food residues in addition to the one studied here (agar) which are highly hygroscopic.

Finally we are well aware of other properties of foods that render them laxative. The effectiveness of the soluble juices of apples and pears and other raw fruits has never to our knowledge been accurately studied. Nor has the well known laxative quality of dried prunes and figs been identified. Certainly we have presented evidence for the stimulating effects of sugars and starches when they predominate in the diet.

The physician should be aware of all these facts and make use of them when he feels it is for the benefit of his patient that the volume of the stool should be increased.

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OBSERVATIONS ON THE USE OF ACETYL BETA METHYLCHOLINE CHLORIDE IN CHRONIC ARTHRITIS ¹

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MANY investigators have studied the value of choline compounds in the treatment of conditions involving vascular spasm. Acetylcholine has long been known but, because of its nicotine-like action, is not suitable for therapeutic use. Major and Kline¹ synthesized acetyl beta methylcholine chloride, a more stable compound, free from the nicotine-like side effects of previous compounds. When Starr² compared the action of acetyl beta methylcholine with acetylcholine, he found they had similar effects on the cardio-vascular system of animals when given intravenously. He also found acetyl beta methylcholine chloride more than 10 times as active as acetylcholine when given hypodermically in normal man, and in addition it could be given orally. Moreover, it lacked many of the undesirable side effects of acetylcholine. Starr believes acetyl beta methylcholine to be a superior choline compound and that it should replace acetylcholine for therapeutic purposes.

The pharmacologic reactions due to acetyl beta methylcholine are prompt and vigorous, and are similar to those which follow stimulation of the parasympathetic nerves. There is well marked peripheral vasodilation. This latter action has been investigated as to its value in conditions accompanied by, or due to vascular spasm. We undertook this present problem to ascertain the effect of acetyl beta methylcholine on the peripheral circulation. A group of 25 patients from the arthritis clinic of Northwestern University Medical School was selected. Although we are not convinced that there is a causal relation between the circulatory changes in arthritis, and the joint lesions, we do know that circulatory disturbances accompany and aggravate the disease. This has been shown by Pemberton³ and others.

We realize the pitfalls attendant on the therapeutic study of this drug. This is particularly true in a field where measurement of success must depend on vague subjective changes and factors which are difficult to measure with accuracy. We have attempted to obtain objective measurements of observed changes after use of the drug, and to control these measurements under as nearly uniform conditions as possible, by identical observations on the same or similar patients on whom various types of therapy were used.

Acetyl beta methylcholine has been given to patients orally, subcutaneously and more recently by common ion transfer. When given by mouth the drug has a much milder effect and requires much larger dosage.

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than is suitable for subcutaneous administration Goldsmith⁴ gave 50 to 150 milligrams by mouth without profound or uniformly appreciable effect on the blood pressure or pulse rate Its action, when taken by mouth even in large dosage, was strikingly less effective than that produced by a 20 milligram dose given subcutaneously in the same patient

Acetyl beta methylcholine is prompt and vigorous in action when given subcutaneously Starin² states, "Its physiological activity is very great, being of an order similar to that of adrenalin or histamine" The striking systemic effects of the drug are a fall in blood pressure a rise in pulse rate, flushing of the face and neck, sweating and salivation This appears quickly, in one or two minutes after injection, and terminates in 15 or 20 minutes It produces a constricting effect on the bronchioles, and transient asthmatic attacks have been produced by this drug in those susceptible Its use also seems contraindicated in hypotension and in serious cardiac disease (except for its usefulness in attacks of paroxysmal tachycardia) In our series, we treated two cardiac patients, one of whom developed syncope and required atropine for relief, and the other suffered an aggravation of anginal pain The former patient had a chronic rheumatic carditis, the latter had a coronary lesion The drug should not be given intravenously because heart block may occur, particularly if the dosage is large (Katz⁵) Realizing this danger, we have not given acetyl beta methylcholine intravenously We have seen no evidence of heart block in this series, giving the drug by common ion transfer If untoward reactions do develop atropine abolishes the action of the drug almost immediately We have found it necessary to use atropine only once,—in the cardiac patient mentioned above

We gave acetyl beta methylcholine to our group of patients by the common ion transfer method, which in effect gives a slower, more gradual absorption from the superficial tissues The constitutional effect of the drug appeared and in addition there was obtained a striking local reaction consisting of increased skin temperature, sweating, gooseflesh, faster capillary flow⁶ and a diffuse pinkness of the skin over the area covered by the positive electrode This reaction, we feel, is quite different from and more lasting than that of local counter-irritation We feel that our controls (chart 1) demonstrate that it is definitely a local drug effect This local effect at times lasted for 12 to 24 hours We consistently found a decreased skin temperature distal to the treated area, whereas proximal to the treated area we always observed a rise in skin temperature of 2 to 4° F This makes it necessary, when local effect on the hand is desired, to apply the positive electrode on the hand itself and not on the forearm proximal to it (figures 1, 2, 3) These marked local effects furnish the rationale for the use of acetyl beta methylcholine in this manner in arthritis

We found that the drug consistently produced characteristic general reactions, which included a fall in blood pressure, averaging 12 millimeters of mercury and a rise in pulse rate averaging 22 beats per minute Respiratory rate was unchanged, but most patients described a sense of heaviness in

CHART I
Table of Average Measurements and Reactions

Methods	Skin Temperature °C					P	R	Rectal Temp	Pulse Vol Wave	Reaction	
	Pre-iced	Distal	Proximal 2"	Proximal 5"						Local	General
Mecholyl	96	82	94.3	92.4		22	Deeper	No	Increase 3 X +	Heat, redness, sweating	Salivation, sweating, heat, perspiration
Histamine	94.3	83	92.5	91.5						Redness, wheals	None
Heat lamp									Increase -2 X		
Diathermy									Unchanged	Increased heat	None
Calvarianism	96	93				0			Unchanged	Redness, heat	Sl perspiration
Mecholyl (Hypo)							Labor		Unchanged	None	Profound disturb, cold extremities, labored resp, sub sternal press
Polar reversal mecholyl		93				0	0	0	Unchanged	Sl local heat	Sensation heaviness limb

<i>Right Knee</i> 12-14-34				
Time	Skin Temp Rt Thigh	Blood Pressure	Pulse	General Reaction
3 05	91 0	125/80	88	Temp mouth
3 10	91 0			5 M A Prickling sensation + Electrode
3 15	92 0	128/78	100	25 M A Salivation lacrimation
3 20	92 8	122/80	112	30 M A Salivation ++ Flushed cheeks
3 25	93 1	124/78	112	40 M A Sweating
3 28				Tremor Feels she is having a chill
3 30	93 2	126/75	112	Fine tremor leg muscles continuing
3 35	92 9	124/92	96	Current off
3 40	92 5			Skin + Electrode red feels hot but temp
				87 Rt 87 Lt
				2nd treatment area + Electrode Before 87° F
				After 91 4° F
				Rise 4 4° F

FIG 1 Characteristic general and local reaction after acetyl beta methylcholine by ionization

<i>Left Knee</i> 12-7-34				
Time	Temp Skin Dorsum Lt Foot	Blood Pressure	Pulse	General Reaction
2 30	92 2	132/80	80	Knee painful, swollen limited motion
2 33	92 3		80	
2 35	92 4	122/80	80	5 M A Current
2 40	92 5	120/80	84	40 M A Heat at + Pole
2 50	92 5	118/78	93	50 M A + Nasal secretion
2 55	92 5	100/63	90	50 M A Sl flushing
3 00	92 2	105/65	88	Current gradually off
3 07	92 0			Very little general reaction

FIG 2 Less striking general reactions to acetyl beta methylcholine by ionization

Galvanic Current Without Mecholin

- Rt Elbow + Pole

5-16-34

Time	Skin Temp Rt Forearm	Blood Pressure	Pulse	General Reaction
10 45	92 3	98/?	54	
11 00	93 5	98/?	54	Saline solution + Electrode
11 15	92 5	98/?	54	Current on
11 30	93 2	98/60	54	30 M A No reaction
11 45	93 5	98/60	58	40 M A No reaction
12 00	93 8	98/70	68	No reaction
				Perspiration only
				Temp over treated area
				96 1 After current
				93 1 Before current

FIG 3 Control reactions using galvanic current without acetyl beta methylcholine

the chest and inspired deeper. A flushing of the face, neck and ears occurred in all who experienced general reactions. Perspiration was usually marked, particularly about the face and neck, even in those who claimed to have had no perspiration in several years. Increased salivation and occasionally

lacrimation lasted one to two hours. One patient had increased saliva after each treatment for 12 to 24 hours. Body temperature by rectum, taken by mercury thermometer and by thermocouple, showed no change.

The general changes described are similar to those which follow subcutaneous injection, with the striking difference, however, that the effects came more gradually, caused much less distress and lasted longer. For our purpose the added local effect was a distinct advantage.

The reactions noted are specific ones due to drug action and not to current or heat effect. We have used the same technic in the same patient without acetyl beta methylcholine and none of the characteristic effects ascribed to the drug were observed. Further attempts to control this were made by local use of diathermy, infra red, and by reversing the current with the drug under the negative electrode. In none of these did we produce any general reaction, and the local effect of these heating agents was obviously less in degree and of a more transient nature.

Technic. We used a vacuum tube rectified direct current which gave a fairly smooth galvanic current (figure 4). The active electrode consisted of an asbestos fabric (resistant to tears) saturated with a 1 per cent solution of acetyl beta methylcholine chloride. Lower concentrations of the drug were tried, but we did not obtain satisfactory reactions with less than a 1 per cent solution. Kotkis and his associates,⁶ working with dogs, reported no difference in drug effect with 1-1000, to 1-8000 solutions. They did, however, cover a relatively larger percentage of the skin area but did not mention the effect of stronger (1-100) solutions. We found a decided difference between the reactions obtained with a 1-100, and with a 1-200 solution. The weaker solution gave none of the clear-cut reactions illustrated in figures 1 and 2. The saturated fabric was wrapped in close contact about the part to be treated, and then a metal foil strip, three-eighths of an inch in width, was wound spirally about the saturated paper (figure 4). This metal strip was used to conduct the galvanic current evenly over the whole area. The positive pole of the galvanic current source was connected to the distal end of the metal strip. The negative pole of the machine was connected to the patient's back by means of a large dispersive electrode, 10" by 12" in size. This completed the circuit. The strength of current and the time of the current flow regulates the effectiveness of the ionization. We fully realize the limitations of introducing ions into living tissues by this method. Individual tolerance to the treatment guided us somewhat in the current strength, but we were usually able to give 40 to 50 milliamperes for 20 minutes after the first treatment. When the treatment was started, the current strength was gradually raised until the desired milliamperage was reached. Sudden increases should be avoided. At the end of treatment, the current intensity was gradually reduced until no current flowed. Following treatment the patient should remain quiet and warm for 30 to

60 minutes and then be allowed to resume his usual activities. When many joints are involved we have found it better to concentrate treatment on one joint or limited area,—such as the hand. The most satisfactory

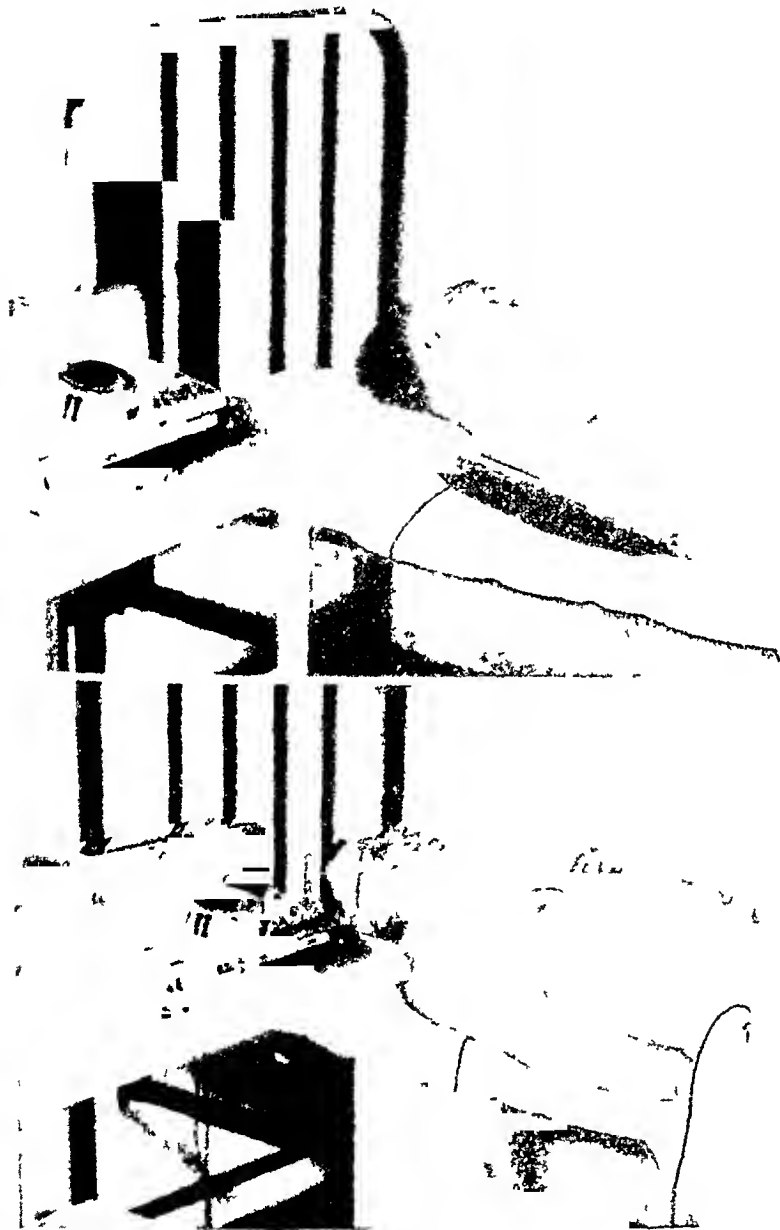


FIG 4 Method of applying negative (above) and positive (below) electrodes for ionization of acetyl beta methylcholine

interval between treatments appeared to be three or four days. The therapeutic effects on patients were studied after five, 10, 15, and 20 to 25 treatments. As a result of this check, we found the maximum effect was achieved after 18 to 20 treatments.

Acetyl beta methylcholine can produce undesirable reactions. Dosage when given subcutaneously must be accurate. One physician gave a subcutaneous dose of 250 milligrams of acetyl beta methylcholine which was 10 times that recommended as maximum. His patient had a severe reaction, but survived. Regardless of how this drug is given a hypodermic of atropine gr 1/100 should always be prepared and available for use. Heart block can easily be produced in dogs, but they usually recover without atropine. These unfavorable reactions are minimized when the drug is given by common ion transfer. We have not had any very serious reactions, nor have we heard of any fatalities from its use. It is a drug of quick, powerful reactions, however, and should be as much respected as epinephrine.

We have treated 27 patients in the manner described during the past two and one-half years (chart 3). Earlier we made no attempt to select patients, as to the stage or type of their arthritis. It was soon evident, however, that certain less advanced arthritics derived more benefit than the far advanced. One would expect this, and it proved to be true in both the rheumatoid and osteoarthritic patients. Those with evident circulatory disturbances of the extremities—those with cool, pale, moist, and often cyanotic hands and feet—seemed to gain most from the treatment. All of our patients had had considerable previous medical treatment along the usual lines without much evident improvement. Acetyl beta methylcholine is not useful in those arthritic patients with peripheral arteriosclerosis nor is it feasible to treat patients with well distributed skin changes. It seemed most helpful in those who (1) show the earlier changes of the rheumatoid type, with cool, damp and cyanosed extremities, (2) have moderate hypertrophic changes with paresthesias and sensitivity to cold, and (3) have sciatica or other manifestations of spinal nerve root irritation as a result of spinal arthritis.

In an attempt to gain objective evidence of the changes taking place, we have measured the pulse volume waves in the limb under treatment. These pulse volume wave changes were recorded graphically by the Johnson plethysmograph (chart 1). The graphic records, taken on the fingers before and after treatment of the hands, show an increased wave deflection, which is apparently dependent on the ability of the blood vessels in the studied part to dilate with each heart beat. Many cases of arthritis thus studied showed a surprisingly flat wave, as is illustrated in chart 2. One patient with a well marked peripheral arteriosclerosis showed a very small pulse volume wave both before and after acetyl beta methylcholine. Usually, however, the dilation of the vessels, as measured by the pulse volume wave, was increased after application of the drug (figure 5). We tried to keep conditions of the room and patients uniform in taking records. Although we did not have a constant temperature air-conditioned room, room temperature was taken into consideration. We consider this pulse volume wave record a better index of improved circulation in an arthritic member than observations of capillary changes in the nail fold. We do not believe that

FINGER VOLUME CHANGES .

Plathysmograph Records











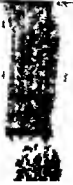




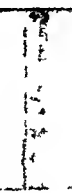
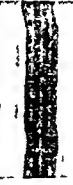

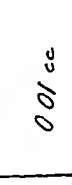
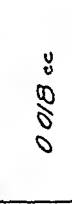
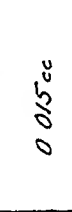
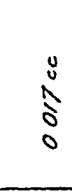
Patient	Mecholyl Application		Control Applications		
	Before	After	Before	After	
Melville	 0.005 cc	 0.02 cc			
Bacherz	 0.005 cc	 0.0125 cc	 0.003 cc	 0.003 cc	Heat Lamp
Wagenstein	 0.005 cc	 0.013 cc	 0.003 cc	 0.003 cc	Mecholyl hypodermic
Grundy	 0.005 cc	 0.02 cc			
Brown	 0.003 cc	 0.003 cc	 0.003 cc	 0.003 cc	Galvanism Only.
Jermyn	 0.003 cc	 0.015 cc			
Atkins	 0.01 cc	 0.013 cc	 0.015 cc	 0.017 cc	Diothermy.

CHART II Comparative finger volume changes with various types of treatment

CHART III
Summary of Patients Treated, and Results

Patient	Age	Diagnosis	Duration of Disease	Complaint	Number of Treatments	Pain	Result Motion	Fatigue	Reactions		Complications	Duration Relief	Remarks
									Local	General			
M	56	Hypertrophic arthritis	7 years	Pain stiffness paresthesia fatigue	15 hands	Decrease	Increase	Disappeared	++++	++	Menopause	8 months	
U	50	Hyper arthritis, sciatica	3 years	Pain right hip sciatic fatigue	21 sacral area	Relieved		Disappeared	++++	++	Myocarditis, secondary anemia	1 year	No interval treatment since other treatment since Strong and well
T	30	Infectious arthritis	2 1/2 years	Pain stiffness fatigue	19 hands and knees	Decrease	Increase	Decreased	+++	++	Secondary anemia, chronic tonsillitis	1 year	
J	24	Infectious arthritis	9 years	Total disability	19 hands	No effect			++	++		None	Disease too far advanced Bone changes Candidate for reconstructive surgery
G	35	Infectious arthritis	5 years	Pain stiffness left elbow	21 elbow	No effect			+++	++	Secondary anemia	None	May be gonorrheal arthritis
D	23	Infectious arthritis	2 mos	Pain, swelling, paresthesia wrists	17 hands	Relieved	Increased	Decreased	++	++	Obstinate constipation	10 months	
C	12	Infectious arthritis	3 years	Pain stiffness polyarticular	27 hands and knees	No change			+++	+++	None	None	
K	40	Infectious arthritis	2 1/2 years	Pain stiffness polyarticular	7 hands	Slight improvement	Stopped treatment		+++	++	None		Stopped treatment
G	53	Mixed arthritis	5 years	Swelling pain knees	12 knee	No improvement			0	0	None		No reaction to drug
S	35	Infectious arthritis	many years	Polyarticular pains stiffness	6	None	Stopped treatment		++	++	None		Did not continue treatment
S	39	Infectious arthritis	10 years	Polyarticular pains deformities	20 hands	No change	Increased	Marked decrease	+++	+++	None	6 months	Gained weight, strength use hands
S	51	Infectious arthritis	14 years	Pain, swelling fingers knees, shoulders	14 knees	Little change			++	+	Menopause, chronic infected tonsils	None	Stopped treatment

CHART III—Continued

Patient	Age	Diagnosis	Duration of Disease	Complaint	Number of Treatments	Pain	Result Motion	Fatigue	Reactions		Complications	Duration Relief	Remarks
									Local	General			
B R	64	Infectious arthritis advanced	20 years	Polyarticular pains de formities	16 hands	Unchanged	Increased	Unchanged	+	+	None	None	Never able to take adequate current for full drug effect
L H	53	Hypertrophic arthritis	3½ years	Pain stiffness weakness hands	15 hands	Decreased	Increased	Decreased	++	++	None	3 months	Marked increase in flexibility and use of the hands fingers
L G	68	Hypertrophic	16 years	Pain stiffness knees and hands	16 knees	No change	Increased	Decreased	+++	++	Scintill	10 months	Stronger, more alert
O B	48	Hypertrophic	Many	Paresthesias of fingers	20 hands	Decreased	Increased	Decreased	+	+	Gastric ulcer	1 month	
D B	30	Infectious	5 years	Low back pain, cold extremities	11 knees	Disappeared	No change	Decreased	++++	++	Obesity		Severe reaction Required atropine
S W	48	Hypertrophic	20 years	Pain hands and knees	16 hands	No change	No change	No change	+++	+	Psychoneurosis		
F R	61	Hypertrophic	3 years	Pain paresthesia of lower extremities	17 knee	Decreased	Increased	Disappeared	++	++	Chronic prostatitis	5, all under treatment	Paresthesia and fatigue markedly relieved
L W	31	Infectious	4 years	Fatigue pain knees and back	13 knee	Disappeared	Increased	Disappeared	+++	+	None	Still under treatment	Four years medical treatment and no relief. Se cured marked relief
G R	39	Hypertrophic	3 years	Low back pain also referred to scapula	19 low back	Decreased	No change	No change	++	+	Constipation proctitis	Still under treatment	Severe pain entirely relieved with few treatments
O B	40	Hypertrophic	3 years	Pain stiffness to hands and knees	8 hands	No change	No change	No change	+	++	Psychoneurosis		
A D	34	Infectious	?	Pain knees	8 knees	No change	No change	No change	++	+	Dementia praecox		
K B	44	Infectious	6 years	Pain swelling hands and elbows	23 hands and knees	Decreased	Increased	Disappeared	+++	++	None	10 months	
H B	56	Infectious	?	Pain and deformity of hands	2 hands	No change	No change	No change	+++	+	Coronary sclerosis		Unable to continue treatment due to cardiac condition

a convincing characteristic capillary bed picture has been presented in arthritis

Many patients showed not only a marked pulse volume wave increase in the member treated locally by common ion transfer but also minor increases in pulse volume wave in the opposite untreated member. Arthritics with cool, clammy hands showed in the first instance an almost flat curve, and

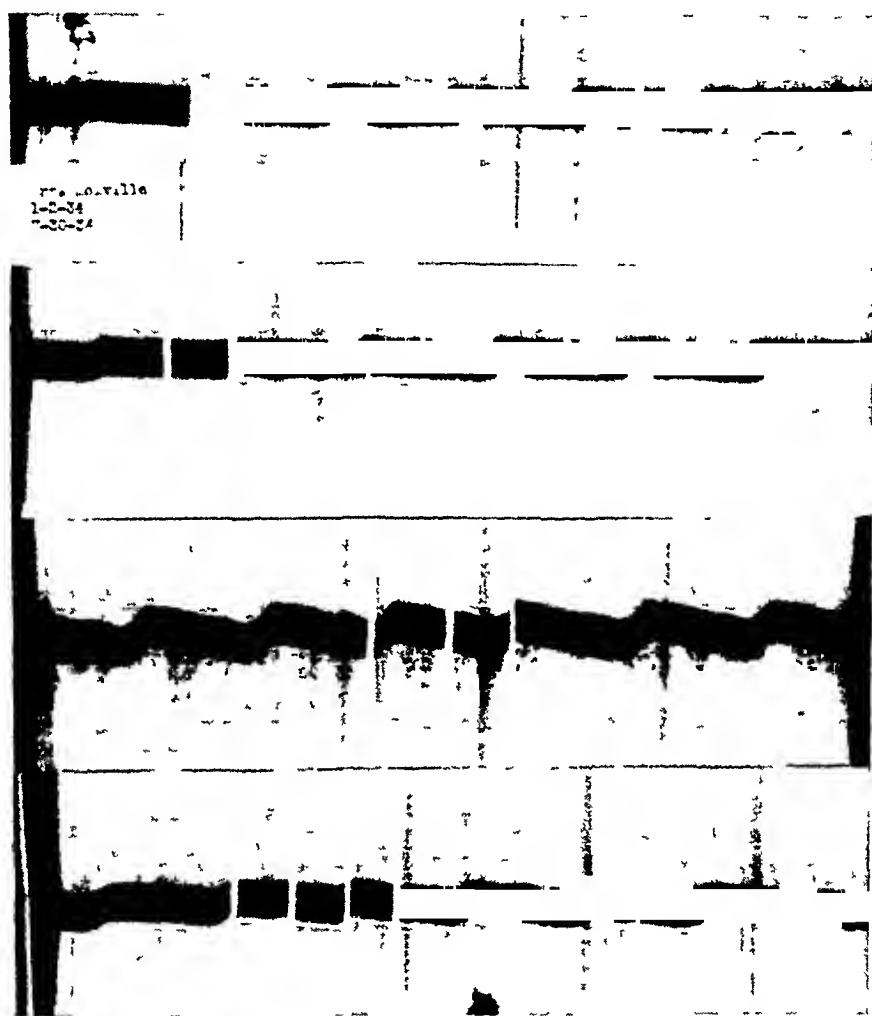


FIG 5 Pulse volume wave of index finger (A.M.) before (I) and after (111) acetyl beta methylcholine applied to the hand

after acetyl beta methylcholine a striking increase in the waves (figure 5). Given subcutaneously, the drug did not cause local changes in circulatory volume.

In the patients on whom control observations were made, the pulse volume waves were of a lower amplitude.

The well known cycles of improvement of arthritics and the lack of any well-defined measurable factors, make evaluation of therapy hazardous.

The recording of decreased pain and increased motion in function rests too largely on the patient's interpretation of his subjective sensations. With patients under continuous observation one can judge fairly well the extent of clinical improvement, but this rather intangible judgment is difficult to present to others. Nevertheless, we can offer no better measure for evaluating the present group.

The hands treated showed in 8 of the 14 patients an increased flexibility in function and usefulness in work. A patient, for example, who previously had been able to lift her coffee cup to her mouth only by using both hands, was able to do this with one hand in a normal manner. Another, forced to give up her work as a clerk and unable to do sewing, became able to work and sew again four days a week without discomfort for continuous periods of an hour or more. A young woman with considerable pain, stiffness and weakness in her hands who had been unable to do her housework for two years, reported a decided decrease in joint pain, improved motion, and a marked increase in strength. She became able to do all her housework except scrubbing floors and ironing. An older woman with lumbar and sacro-iliac arthritis, who complained of aching pains and constant fatigue to such an extent that she was comfortable only in bed, was treated over the area of her discomfort with the usual general reaction. After treatment, the low backache largely disappeared, "she felt quite strong again and was not so tired." Four months later without further treatment, she was much stronger, and without undue fatigability. A medical student observed an increased flexibility of the hands, a loss of considerable morning fatigue and joint stiffness, became much less tired and resumed walking and other outside activities. He noted the effect of the drug for three or four days following each treatment.

The group of failures in treatment were in general the elderly, far advanced rheumatoid arthritics with bone changes and fibrosis. In such advanced degrees of the disease much relief cannot be expected.

Striking relief of pain was afforded some cases, but as a record of therapeutic achievement in this respect, our results are only fair (chart 2). The striking therapeutic effect in the group is the decreased fatigability, and the increased endurance. This was consistently noted in almost all patients who absorbed the drug and took a sufficient number of treatments. Several patients resumed their normal activities, spent less time in bed, and carried on more work and play without increase of pain, stiffness or fatigue. This improvement in the endurance of our patients was called to our attention voluntarily and spontaneously, it being an unanticipated effect. We have not noted such a relief from fatigue under other forms of treatment. That this is a vital factor in the lives of most arthritics is constantly borne out by the complaints of most patients. Most workers in this field agree that rest sufficient to relieve fatigue is a most important element in the treatment of arthritic patients.¹⁰

Acetyl beta methylcholine does relieve fatigue in a large percentage of arthritic patients who are able to take adequate dosage. Whether this is due to its vasodilator effect, or some more direct effect on muscle, we do not know.

It is interesting that Hench¹¹ and his associates at the Mayo Clinic have treated this fatigue factor with amino-acetic acid and ephedrine. They report striking effects in certain patients, no effect at all in other apparently similar cases. No satisfactory measure of such fatigue has been proposed, though indirectly metabolic studies may help. It has not yet occurred to us how this factor may be measured. We believe that if fatigue can often be controlled, in many instances pain can be relieved, physical activity increased, and the morale of these patients raised considerably. It is this effect of mecholyl that impressed us most, and the prevalence of so many tired, physically restricted arthritic patients makes the continued use and study of the drug worth while.

CONCLUSIONS

1 Twenty-two cases of arthritis have been treated with acetyl beta methylcholine common ion transfer.

2 Eight of 14 patients whose hands were treated showed an increased flexibility in function and usefulness in these hands.

3 Pain was relieved in some cases.

4 Muscular fatigue was markedly relieved in almost all cases adequately treated.

5 Increased endurance was experienced by those completing the course of treatments.

6 Circulatory changes were graphically shown.

7 The group of failures were in general the elderly patients with far advanced rheumatoid arthritis with bone changes and fibrosis.

8 Patients with circulatory disturbances of the extremities, those with cool, pale, moist, and often cyanotic hands and feet gained most from treatment.

9 Maximum effects were gained after a series of 18 to 20 treatments.

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STUDIES IN HODGKIN'S DISEASE

III CLINICAL APPLICATION OF THE GORDON TEST (A SYNDROME OF ATAXIA, SPASM AND PARALYSIS INDUCED IN RABBITS BY THE INTRACEREBRAL INJECTION OF EMULSIFIED HODGKIN'S TISSUE)'

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THE description by Gordon^{1,2} in 1932 of a biological test for Hodgkin's disease aroused widespread interest. Van Rooyen³ in Scotland made a trial of the test and later, in a paper published in this country, van Rooyen and Olgivie⁴ expressed the opinion that it had proved itself to be of definite clinical value. Our own evaluation of this test as a diagnostic aid in the differentiation of the Hodgkin's type of lymphoblastoma is presented here after three years of experience in which material from 16 cases of Hodgkin's disease and 30 cases of other types of lymphadenopathy has been tested.

Gordon's test consists of the injection of a saline or broth emulsion of lymph node tissue into the cerebrum of the rabbit. A positive test appears three or four days after such an injection when the animal loses weight, develops ataxia, stiffness of the legs and neck, spasticity and has convulsions on stimulation. If the animal survives, these signs of cerebral disease may disappear in two to four weeks leaving it quite normal, again animals may survive for weeks in the chronic active state and gradually develop paralysis of the hind quarters or even a quadriplegia. The above syndrome is not peculiar to the rabbit alone, nor is the reaction specific for Hodgkin's tissue. Kelser and King¹¹ have obtained a similar response in the guinea pig using both bone marrow and Hodgkin's tissue, and Friedemann⁵ has pointed out that the proteolytic ferment of Jochmann⁹ and his own acetone-alcohol-ether extract of normal human spleen, bone marrow or leukocytes may provoke a similar reaction.

METHODS

The specimens were obtained personally at operation, placed in a sterile Petri dish and taken to the laboratory. Here the extracapsular tissue was cleaned away under aseptic precautions and a transverse section, usually including one-third of the node, was removed for routine pathologic section. Another third of the node was cut with scissors into small bits and the tissue ground in a mortar with sterile normal saline or meat broth of pH 7.4. This heavy emulsion (approximately 15 per cent) was then cultured on aerobic and anaerobic media and part of the supernatant fluid

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immediately injected into the brains of rabbits. Cultures of the emulsions usually showed no growth but in a few, colonies of staphylococci or common contaminants appeared. Pure broth cultures of these organisms when injected into rabbit's brains did not produce a positive test. The remaining third of the lymph node and the unused portion of the emulsion were then stored at 5 to 10 degrees Centigrade.

Injection of the rabbit was done under ether anesthesia. With a small two-edged hand tool the skull was trephined at the angle formed by the junction of the occipital and central longitudinal ridge. This exposed relatively silent areas of the occipital lobe into which 0.35 to 0.45 c.c. of the emulsion was slowly injected. The skin wound was closed with Michel's clips and the animal returned to the cage. Following this the animals were weighed daily and watched for signs of a positive test.

Extracts of biopsied nodes and of bone marrow, liver and spleen obtained at autopsy were also made, using the method described by Friedemann.⁵ The tissue was extracted in a mortar with acetone and at the end of 15 minutes the undissolved material was collected on filter paper and washed first with absolute alcohol and then with ether. The residue was allowed to dry and then mixed with an equal volume of 33 per cent glycerin in saline. After standing 24 hours the undissolved material was spun down and the supernatant glycerin mixed with five times its volume of a 2:1 alcohol-ether mixture. The resulting precipitate was allowed to settle out and then taken up in saline for injection.

RESULTS

Table 1 shows the control series including lymphosarcoma, reticulum cell sarcoma, lymphoblastoma type undetermined, giant follicular lymphoma, hyperplasia, chronic inflammation, metastatic epidermoid carcinoma, mixed

TABLE I
Tissues Used as Controls for Gordon's Test

Diagnosis	Number of Cases	Rabbits Injected	Gordon's Test
Lymphosarcoma	10	20	20 Negative
Reticulum cell sarcoma	5	10	10 "
Lymphoblastoma? type	1	2	2 "
Giant follicular lymphoma	1	2	2 "
Hyperplasia	4	10	9 "
Chronic inflammation			1 Positive
Epidermoid carcinoma	4	8	8 Negative
Mixed tumor of parotid	3	6	6 "
Dermoid cyst	1	2	2 "
Fetal tissue	1	2	2 "
Pseudo tumor of orbit	1	1	1 "
	32	65	64 Negative 1 Positive

tumor of the parotid, dermoid cyst, fetal tissue and pseudo-tumor of the orbit. In all, 65 rabbits were injected with material from 32 patients. In only one case was a positive test obtained. This was from an emulsion of a lymph node from a seven year old girl who had an enlargement of the cervical and inguinal nodes for three years. The clinical impression was that she had Hodgkin's disease and, therefore she had received roentgen-ray treatment two years before entry. The nodes then decreased in size but had enlarged again during the year previous to coming into our clinic. A biopsy was done in the hope of establishing a diagnosis of lymphoblastoma but the pathological report was hyperplasia. Of three rabbits injected two remained normal while the third developed a weakly positive test. The diagnosis in this case is still uncertain, but 10 months after biopsy she was clinically in the end stages typical of Hodgkin's disease. Except for this case and one case of reticulum cell sarcoma the patients in the control series had received no roentgen-ray therapy before biopsy of the lymph node.

Gordon² remarked that this encephalitogenic agent was diminished or absent in fibrosed Hodgkin's glands but van Rooyen,³ with whom we agree, could find no significant differences in the histologic structure of nodes giving a strong, weak or negative test.

Table 2 summarizes the results of tests with material from 16 untreated patients whose biopsied lymph nodes showed the histologic appearance typi-

TABLE II
16 Hodgkin's Tissues Used in Gordon's Test

	Number of Cases	Rabbits Injected	Gordon's Test	
			Positive	Negative
Cases having at least one positive test	9	58	46	12
Cases having all negative tests	7	21	0	21

cal of Hodgkin's disease. These 16 patients entered the hospital for the diagnosis of enlarged lymph nodes, often in one or both sides of the neck. They were usually young people (average age 26 years) who had noted the appearance of the masses from one month to two years before entry (average duration 5 months). In nine (56 per cent) of these cases the tests gave results which were considered positive while in seven the results were negative. However, in five of the nine one or more of the injected rabbits showed no reaction. In the other four cases all animals were positive. Van Rooyen⁴ reports 75 per cent of all Hodgkin's cases as giving a positive test while Hanson⁷ and van der Hoeden and Hulst⁸ each report 60 per cent. Goldstein¹² found the test positive in seven of nine cases of Hodgkin's disease.

It is of interest at this point to note that in none of the other types of lymphoblastoma was a positive test obtained, in contrast to the finding of positive tests in over half the cases of the Hodgkin's type. This lends support to the belief that Hodgkin's disease may be separated from the lymphoblastoma group as a distinct entity.

THE NATURE AND PATHOLOGY OF THE ENCEPHALITOGENIC AGENT

The properties of the agent producing these reactions in the rabbit have been investigated by Gordon,¹ MacKenzie and van Rooyen⁶ and Kelser and King¹¹ and our observations here are in accord with theirs. Transmission of the agent from rabbit to rabbit was not effected and repeated injections of inert material did not sensitize rabbits to later injections of Hodgkin's material that had proved to be negative in rabbits that had not been previously injected. Evidently no immunity to the agent was produced as animals rendered positive and allowed to recuperate again became positive on injection of a second active emulsion. Likewise the serum of previously positive animals when added in equal quantities to an active emulsion did not inhibit the encephalitogenic factor.

The agent is remarkably stable. After preservation for 24 and 26 months at 5 to 10 degrees Centigrade and being considerably desiccated, two Hodgkin's nodes were emulsified and produced definitely positive Gordon tests. After exposure to 70 degrees Centigrade for one hour the agent loses its activity. The active principle is extracellular as cell free supernatant fluids give positive tests. The agent in saline emulsions could not be passed through a filter (Berkefeld N) and application of the emulsion to the scarified cornea of rabbits provoked no signs of either encephalitis or keratitis. Recently van Rooyen⁶ has found that the maximum effect of the agent is obtained if the broth is adjusted to a pH of 6.8 to 7.3 and that by so adjusting the Seitz and Berkefeld candles he could successfully pass the agent through the filter. It is well known that meat broth itself will change the retentiveness of a Berkefeld filter,¹⁰ so that this may in part explain his results.

Friedemann⁵ recalled that this reaction of the rabbit after the injection of Hodgkin's gland emulsion was not specific, as Jochmann and Lockemann⁹ had found a proteolytic ferment in extracts of normal spleen, white blood cells and bone marrow of man and monkey that produced identical effects in rabbits. Friedemann's modified technic, the acetone-alcohol-ether extract described here under methods, has also yielded an encephalitogenic factor that produces positive Gordon tests. Friedemann assumed that a virus or bacteria could not withstand such processing, but MacKenzie and van Rooyen⁶ have since found that it is not necessarily lethal to certain bacteria. In addition to the tissues mentioned above we found that such an extract of normal human liver would produce a positive test.

From two cases of Hodgkin's disease both the broth emulsions and the acetone-alcohol-ether extracts of diseased nodes gave typical positive Gordon tests while from a third case neither caused a reaction in the rabbits. From three control cases (reticulum cell sarcoma, lymphosarcoma and lymphoblastoma type undetermined) neither the emulsions nor the extracts caused any reaction in rabbits.

The exact nature of this agent is still unknown but as shown above it lacks many of the characteristics of a virus. Gordon mentioned the similarity of the reaction to the meningo-encephalitis produced by the virus of dermo-vaccine, herpes and psittacosis and the remarkable stability, like the virus of swine fever. In a recent publication MacKenzie and van Rooyen⁶ found that the proteolytic ferment of Jochmann could be identified separately from the agent obtained by the methods of Gordon and Friedemann. As indicated in the six cases last mentioned the agent can withstand rather drastic extraction with acetone-alcohol-ether and what is more important, it is not present in lymph nodes giving a negative Gordon test.

Autopsies were done on rabbits killed with ether. Those found dead in their cages were not examined. The brains usually appeared normal in the gross except for some hyperemia about the site of injection, although in two gross signs of meningitis were found. Cultures of the injected areas yielded no growth and no evidence of the parasite *Encephalitozoon cuniculi* could be found. Microscopic examination showed changes, usually in one or both hemispheres. A perivascular infiltration of mononuclear cells resembling monocytes and lymphocytes was the predominant lesion but meningeal infiltration and occasional focal collections of these large mononuclear cells were observed. While these changes were observed in all the positive cases they were very slight in three animals and a slight meningeal reaction was present in several of the negative ones. Consequently it is felt that no definite conclusions can be drawn as to the significance of the findings. One can probably go so far as to say that the changes observed, because of the inconspicuous microglial reaction, do not resemble the picture commonly found with virus diseases of the brain. The histo-pathologic aspects of the problem invite a more thorough examination of positive animals and careful comparison with a larger number of injected negative and untreated animals.

SUMMARY

From nine of 16 cases (56 per cent) of microscopically typical Hodgkin's disease positive Gordon tests were obtained, but of 58 rabbits injected with material from these nine there were 12 rabbits that showed no reaction. In a control group of tissues from 32 cases of other pathological conditions 31 gave negative tests. In the one control case described the patient may have had Hodgkin's disease and yet two of the three rabbits injected were negative. The encephalitogenic agent which produces this response in the rabbit is not specific for Hodgkin's tissue for it may be extracted from nor-

mal human marrow, spleen, liver and leukocytes. It was not obtained from eight lymph nodes showing hyperplasia or chronic inflammation. Knowledge of this agent is limited but it appears that it is not a virus and as it will withstand acetone-alcohol-ether extraction it may be a non-living substance simply acting as a profound irritant to nerve tissue.

CONCLUSIONS

Gordon's test, if positive, is only of supportive aid in the diagnosis of Hodgkin's disease and if negative does not exclude it. Therefore, this test should not replace the routine pathologic examination of tissue for diagnosis. The absence of the encephalitogenic agent in the first four types of lymphoblastoma (lymphosarcoma, reticulum cell sarcoma, giant follicular lymphoma and lymphoblastoma type undetermined) adds support to the belief that Hodgkin's disease is a separate clinical and pathological entity.

The author is indebted to Miss Helen Roach for technical assistance and to Dr Chas S Kubik for reviewing the pathology of the brain lesions.

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THE COURSE OF HYPERTENSIVE HEART DISEASE

I AGE OF ONSET, DEVELOPMENT OF CARDIAC INSUFFICIENCY, DURATION OF LIFE, AND CAUSE OF DEATH

By NATHAN FLAXMAN, M D , *Chicago, Illinois*

ARTERIAL hypertension is the most common cause of heart disease in adults regardless of race or sex.¹ There has developed in the last two decades especially an overwhelming literature devoted to this subject which, as Crummer² states, has almost buried from our modern view the earlier and fundamental observations. Janeway's³ classical analysis of 870 cases of hypertensive cardiovascular disease (nephritis included) first indicated that the most prominent symptoms associated with hypertension are circulatory and that in the presence of early symptoms of myocardial weakness a better than 50 per cent chance existed that death eventually would be due to myocardial insufficiency. Fahn,⁴ who added greatly in these earlier days to our knowledge of hypertensive heart disease, found that arterial hypertension by its direct or indirect effects on the heart muscle was the chief etiologic factor in approximately three-fourths of the cases of so-called chronic myocarditis.

The present study on the course of hypertensive heart disease was begun on December 31, 1931. In the following four years 1170 cases of hypertensive heart disease were examined and their histories carefully analyzed. Cases with complicating heart disease of other origin such as those with lesions due to syphilis, rheumatic fever, or thyrotoxicosis, or hypertension the result of glomerulonephritis, and cases with insufficient data were excluded. There remained for analysis 623 uncomplicated cases of hypertensive heart disease. The criteria followed for the diagnoses were those approved by the American Heart Association.⁵

The exact duration of the essential hypertension was not known in any of the cases. Only 31 patients (3.7 per cent) had known of the existence of their hypertension for from one to 12 years prior to the onset of symptoms. In this group the average known duration was five years.

The symptoms that indicated the onset of hypertensive heart disease were dyspnea, precordial or epigastric pain or both, palpitation, weakness, persistent indigestion, and marked loss in weight. Only 6.6 per cent of the white patients were below 40 years of age at the onset of symptoms, but 16.6 per cent of the colored patients were below that age (table 1). The largest incidence among the colored patients occurred in the decade from 41 to 50 years (47.6 per cent), while among the white patients the highest incidence fell in the sixth decade, 51 to 60 years (49.7 per cent).

* Received for publication July 20, 1936.

From the Cook County Hospital (1932-1933),¹ the Mercy Free Dispensary of Loyola University Medical School (1933-1934), and the Out-Patient Dispensary of the Mt Sinai Hospital (Service of Dr. Harry J. Isaacs).

TABLE I
Percentage in the Age Groups

Ages	White				Colored			
	M	F	Total	%	M	F	Total	%
21-30	0	1	1	0.3	4	1	5	2.6
31-40	18	9	27	6.3	19	8	27	14.0
41-50	97	28	125	29.1	64	28	92	47.6
51-60	176	38	214	49.7	47	9	56	29.0
61-70	45	18	63	14.6	10	3	13	6.8
Totals	336	94	430	100.0	144	49	193	100.0
	69.0%				31.0%			

The duration of the disease was estimated in 189 known deceased patients from the onset of the first symptom. Later the data on 434 known living patients were studied in order to compare the duration in the deceased and in the living patients (table 2). Of the deceased white 80.8 per cent

TABLE II
Duration of Disease after Onset of Cardiac Symptoms

Duration	Deceased								Living							
	White				Colored				White				Colored			
	M	F	T	%	M	F	T	%	M	F	T	%	M	F	T	%
1 Day-6 Months	52	9	61	51.3	28	12	40	57.2	125	37	162	53.4	47	17	64	52.1
7 Months-1 Year	17	4	21	17.7	12	1	13	18.5	33	9	42	13.7	19	7	26	21.1
2-5 Years	25	7	32	26.9	13	2	15	21.5	69	15	84	27.6	22	5	27	22.1
6-10 Years	2	2	4	3.3	0	1	1	1.4	7	9	16	5.0	3	2	5	3.9
11-20 Years	1	0	1	0.8	0	1	1	1.4	1	0	1	0.3	0	1	1	0.8
Totals	97	22	119	100.0	53	17	70	100.0	235	70	305	100.0	91	32	123	100.0

and of the deceased colored patients 84.5 per cent had died within two years after the onset of symptoms. A comparison with the percentage of living patients who were observed within two years after the onset of symptoms indicated the same ratio, 77.6 per cent of the living white and 82.1 per cent of the living colored patients. The only similar figures available for comparison are those of Janeway³ who reported that the average duration of life in his group of well-to-do patients after the onset of symptoms was four years in men and five years in women.

The symptoms were usually slowly progressive after an insidious onset but the numerous exceptions made attempts to estimate prognoses very difficult. The life-expectancy was short when the symptoms appeared suddenly and were not preceded by any omens of cardiac distress. The average duration of symptoms before the occurrence of heart failure was one year. The main reason for the short interval between the onset of symptoms and the appearance of congestive heart failure appeared to be the sufferers' reluctance to seek available medical attention for the relief of symptoms. Many of the patients continued to work and struggle along in spite of evident heart failure. Some delayed going to bed until the symptoms of failure became so pronounced that they no longer could stand on their feet. Such unnecessary delays led to the death of patients early in the course of the disease.

A comparison of the duration of the disease after the onset of congestive heart failure in the known deceased and in the living patients indicates approximately similar percentages (table 3). Of the deceased white 89.2 per

TABLE III
Duration of Disease after Onset of Congestive Heart Failure

Duration	Deceased								Living							
	White				Colored				White				Colored			
	M	F	T	%	M	F	T	%	M	F	T	%	M	F	T	%
1 Day-6 Months	72	10	82	74.0	41	13	54	78.4	183	51	234	76.9	74	21	95	77.9
7 Months-1 Year	13	4	17	15.2	6	1	7	10.1	26	9	35	11.4	5	7	12	9.8
2-5 Years	6	5	11	9.9	6	1	7	10.1	25	10	35	11.4	11	2	13	10.7
6-10 Years	0	1	1	0.9	0	0	0	0.0	0	1	1	0.3	0	2	2	1.6
11-20 Years	0	0	0	0.0	0	1	1	1.4	0	0	0	0.0	0	0	0	0.0
Totals	91	20	111	100.0	53	16	69	100.0	234	71	305	100.0	90	32	122	100.0

cent and of the deceased colored patients 88.5 per cent had died within one year after the occurrence of congestive heart failure. The percentages of living patients who came under observation within one year after congestive failure occurred were, in the white 88.4 per cent and in the colored patients 88.0 per cent.

As to the age at death in hypertensive heart disease, table 4 indicates that 30.2 per cent of the white and 65.2 per cent of the colored patients had died before they were 50 years old.

The common cause of death was congestive heart failure, as table 5 indicates. Uremia was the next most common cause of death, it was more frequent in the colored patients and in the males of both races. Coronary thrombosis and cerebral hemorrhage were the causes of death of many

TABLE IV
Percentage of the Age Groups at Death

Ages	White				Colored			
	M	F	T	%	M	F	T	%
21-30	0	0	0	0 0	1	0	1	1 4
31-40	4	1	5	4 1	5	3	8	11 6
41-50	25	6	31	26 1	25	11	36	52 2
51-60	52	8	60	50 5	14	3	17	24 6
61-70	16	7	23	19 3	7	0	7	10 2
Totals	97	22	119	100 0	52	17	69	100 0

TABLE V
Percentage of Causes of Death in 189 Cases

Causes of Death	White				Colored			
	M	F	T	%	M	F	T	%
1 Congestive heart failure	63	14	77	64 8	32	13	45	64 3
2 Uremia	13	4	17	14 3	11	3	14	20 1
3 Coronary thrombosis	13	0	13	10 9	2	0	2	2 8
4 Cerebral hemorrhage	3	3	6	5 2	6	1	7	10 0
5 Ruptured dissecting aortic aneurysm	1	0	1	0 8	1	0	1	1 4
6 Spontaneous rupture ascending aorta	0	0	0	0	1	0	1	1 4
7 Adams-Stokes syndrome	1	0	1	0 8	0	0	0	0
8 Diabetic coma	1	0	1	0 8	0	0	0	0
9 Mesenteric thrombosis	1	0	1	0 8	0	0	0	0
10 Incarcerated inguinal hernia	1	0	1	0 8	0	0	0	0
11 Septicemia	0	1	1	0 8	0	0	0	0
Totals	97	22	119	100 0	53	17	70	100 0

patients, especially of those who died within one week after the sudden onset of symptoms. Coronary thrombosis was found to be the third most frequent cause of death. Its highest incidence was in white males (table 6)

TABLE VI
Additional Factors in the 623 Cases

Conditions	White				Colored			
	M	F	T	% of Total (430)	M	F	T	% of Total (193)
1 Coronary thrombosis	29	2	31	7 2	4	1	5	2 5
2 Angina pectoris	13	2	15	3 5	1	0	1	0 5
3 Positive blood Kahn tests	9	4	13	3 0	33	7	40	20 7
4 Cerebral hemorrhage	8	4	12	2 8	11	2	13	6 7
5 Diabetes mellitus	8	3	11	2 5	1	2	3	1 5
6 Obesity	8	1	9	2 1	0	1	1	0 5
7 Sudden death	5	0	5	1 1	1	0	1	0 5
8 Pulmonary tuberculosis	2	1	3	0 7	0	0	0	0

COMMENT

Since an analysis of the course of hypertensive heart disease might not be fairly representative if it were based exclusively on data from the records of deceased patients, there has been included in this study comparative figures drawn from the records of living patients

The short duration of life (two years or less in approximately 80 per cent of the deceased patients) may be accounted for in part by the fact that in the class of patients studied medical attention was not sought until the disease had made marked headway. Janeway, whose series included chiefly patients from the well-to-do, stated that one-half of the whole number of the deceased died within the first five years, one-fourth lived between five and 10 years, and the remaining one-fourth lived over 10 years. Because of the striking variations in the duration of the disease he advised great caution in prognosis. In this series of cases eight deceased patients had lived five to 10 years after the onset of symptoms and we found 26 patients who were living after five to 10 years. Two deceased patients had lived, and seven patients are living 10 to 20 years after the appearance of symptoms.

Two of the deceased patients had lived longer than five years after the onset of congestive heart failure, and at the conclusion of the study there were seven patients living five to eight years after the first appearance of congestive failure.

SUMMARY

The course of hypertensive heart disease based on a four year study of 623 uncomplicated cases (189 known dead and 434 known living) is reported. Approximately 80 per cent of the deceased succumbed within two years after the onset of symptoms. Congestive heart failure occurred most frequently within one year after the onset of symptoms, and 85 per cent of the deceased had died within one year after heart failure appeared. The majority of the deceased colored patients (65.2 per cent) died before 50 years of age, while a minority of the deceased white patients (30.2 per cent) succumbed before that age. Sixty-five per cent of the deceased died of congestive heart failure, although all of the patients had evidence of heart failure at some time during the course of the disease or at the time of death.

A significant number of patients, although very small in comparison with the remainder, had lived or are still living five to 20 years after the appearance of the first symptom, and a lesser group had lived or are living five to eight years after the occurrence of congestive heart failure.

It is a pleasure to express my indebtedness to Dr. Italo F. Volini from whom much encouragement to carry out this study was derived.

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THE PROBLEM OF RHEUMATISM AND ARTHRITIS

REVIEW OF AMERICAN AND ENGLISH LITERATURE FOR 1935

(Third Rheumatism Review)

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This Third Rheumatism Review was prepared at the request of the American Association for the Study and Control of Rheumatic Diseases. The editorial comments express the opinion, not of the Association but of its editorial committee (the authors of the Review) of which Dr. Hench is Chairman.

DURING 1935, medical literature published in English contained over 600 articles on diseases of joints and related tissues and on allied subjects, which have been surveyed for this Third Rheumatism Review. This number is a substantial increase over that of previous years, an increase due in part to the greater amount of investigative work being reported, but particularly to the number of short synopses and reviews presented by physicians to county and state societies. Making few or no pretensions to original researches, many of these papers contained little suitable for this review. But they have a significance not to be overlooked. For the most part they reflect a sound, broadened view of the problem of rheumatism, and provide definite evidence of the growing interest of the medical profession therein. The general practitioner is no longer willing to ignore rheumatism, content with the sorry gesture of salicylates for his new, and spas for his old, arthritic patients. His mind is in ferment, his interest is aroused. His is now a more resolute inquiry, increasingly purposeful and critical. The slogan of the few is becoming that of the many. Something must be done to solve the enormous problem that is "rheumatism."

GENERAL INCIDENCE AND OCCUPATIONAL DISTRIBUTION

Statistics given in previous Reviews^{1,2} show all too well how great a social and economic problem rheumatic diseases are creating. Rheumatic fever and "nonspecific arthritis" were found to be "world problems" in a recent survey on "The Geography of Disease" by the Division of Medical Sciences of the National Research Council.³ Rheumatism apparently knows no boundaries of climate or geography, and few indeed are the countries not widely affected thereby.

Occupational factors play a definite rôle in the incidence of rheumatic diseases, but statistics on the relation of industrial environment to the incidence and course of these diseases have generally been inadequate, according to Buckley,⁴ because neither the patient's occupation nor the exact type of his disease has been carefully classified. Buckley noted that coal miners and others who work underground at warm temperatures and high humidities are much (50 per cent) less subject to atrophic and hypertrophic arthritis than the general male population of Buxton, England, but are much (50 per cent) more prone to fibrositis. Stokers and others engaged in "hot occupations" seem much less susceptible to atrophic or hypertrophic arthritis, rheumatic fever, or fibrositis, but seem prone to gout. Of those reporting to the Devonshire Hospital because of "rheumatism," 8 per cent had gout. A possible cause was considered to be loss of perspiration, an altered saline content of tissue, and changes in the solubility of sodium bismurate. Outdoor workers suffer oftener from atrophic arthritis and from rheumatic fever, indoor workers from hypertrophic arthritis and from fibrositis.

CLASSIFICATION OF DISEASES OF JOINTS AND RELATED STRUCTURES

A general familiarity with terms used by various writers is the first step toward a universal classification of rheumatic diseases. By this token the year's literature indicates some progress. Although writers have continued to use favorite designations, they have with increasing frequency appended the synonyms of others, indicating familiarity therewith. Some have adopted the classification used in our previous Reviews which embodies that approved by the American Committee for the Control of Rheumatism. The year's crop of "new classifications" is small. In general they are but minor modifications of old classifications, or are sometimes proposed without adequate clinical or pathologic foundation to invite our acceptance of them. None seems subject to less criticism than that used in our previous reviews. Hence they will not be copied here to add to the reader's confusion.

Diseases of joints and related structures may be briefly classified as follows: (1) those due to trauma, (2) those due to infections of known type, (3) those of unknown cause but possibly, or probably, due to infection or related toxins, for example, rheumatic fever, atrophic (infectious, proliferative, rheumatoid) arthritis, (4) those of unknown cause and of which the chief characteristic is degenerative change in tissue, for example, hypertrophic (senescent, degenerative, osteo-) arthritis, (5) those of which the chief or only obvious characteristic is some recognizable chemical derangement—a none too well defined group which includes gouty and hemophilic arthritis and the arthritis of serum sickness as well as certain forms of arthritis called "chemical," "metabolic," "allergic," "endocrine," and (6) a miscellaneous group of unclassifiable types. For a detailed amplification of this classification and our own criticism of it and of other classifications the reader is referred to the first review.¹

It would be advantageous for physicians of at least the two great English-speaking nations to employ the same classification. To this end the provisional classification adopted by the Subcommittee on Nomenclature of the British Committee on Chronic Rheumatism is given herewith, and attention is called to their excellent first Report⁵ which includes a full discussion of the pathologic criteria used for this classification.

Group 1 Rheumatic fever, acute (Syn. "Acute Rheumatism") or subacute

Group 2 Acute gout

Group 3 Chronic arthritis

A Rheumatoid type ("atrophic, proliferative")

1 Specific causation Known etiology

(1) Gonococcal arthritis

(2) Tuberculous arthritis

(3) Syphilitic arthritis

(4) Arthritis following other specific infections such as dysentery, scarlet fever, rheumatic fever

2 Nonspecific causation Unknown etiology

(1) With known associated factors

(a) Metastatic or "focal" arthritis, including so-called "multiple infective arthritis"

(b) Associated with disordered metabolism (e.g., gout)

(c) Climacteric arthritis (villous type)

(2) With no known associated factors

(a) Classical type of rheumatoid arthritis of women, usually of child-bearing period

(b) Rheumatoid arthritis in children, including Still's disease

The term "rheumatoid arthritis," when utilized, should be confined to the above two conditions, all other forms being designated "rheumatoid type"

B Osteo-arthritic type ("hypertrophic", "degenerative")

1 Known etiology

(1) Secondary to trauma

(2) Secondary to arthritis of rheumatoid type

(3) Associated with disordered metabolism (climacteric, gout, scurvy, hemophilia)

(4) Associated with organic disease of the nervous system (e.g., Charcot's joints and syringomyelia)

2 Unknown etiology

So-called "senile variety" (e.g., morbus coxae senilis)

Group 4 Non-articular rheumatic affections

DISEASES OF ARTICULAR AND PERIARTICULAR TISSUES RELATED TO TRAUMA

Acute trauma or prolonged or repeated trauma may initiate reactions in articular and periarticular tissues resulting in either an arthritis, synovitis, tendinitis, bursitis, or myositis. The type and extent of the reaction depends on the nature, location and severity of the injury, and resistance of affected tissues and their powers of regeneration. The reaction to trauma to synovial tissue, which has high regenerative powers, will not be the same as that to cartilage, which has feeble powers of regeneration. Trauma may produce arthritis in a previously healthy joint, or it may aggravate a pre-existing arthritis. These two types of traumatic arthritis should be differentiated.

Articular Disease Due Primarily to Trauma When an injury is promptly followed by an acute reaction of swelling, redness, stiffness, muscle spasm and within a relatively short time by roentgenographic changes, a diagnosis of traumatic arthritis is obvious. Diagnosis may be difficult when a delay elapses between injury and the onset of symptoms. Then the question arises whether such an arthritis, manifesting itself after a period of quiescence following an accident, is truly traumatic in origin. According to Bick⁶ a direct blow to an elbow for instance rarely causes immediate damage to cartilage but may disrupt periarticular vessels and produce a vascular disturbance, the cause of later intra-articular changes. Certain criteria for

the diagnosis of traumatic arthritis should control "the well meant but prejudiced testimony of the claimant's physician, as well as the doubts of the impartial or defender's examiner" Bick's criteria follow (1) one should know whether articular function was normal before injury, if the joint was previously affected one must know the degree of previous disability, (2) a diagnosis of traumatic arthritis is not justified in the presence of normal joint function—full painless motion, (3) the presence of pain alone is not enough to justify the diagnosis of intra-articular disease, periauticular disease may account for it, and (4) muscle spasm and definite limitations of motion are generally present Variations from normal range of motion, the presence of any motion not characteristic of a joint, or variations of resistance at the extremes of motion are ipso facto evidence of disease

Not all patients without roentgenographic alterations are malingerers Intra-articular disease may be absent or insufficient in amount to produce them, but periauticular disease (such as rupture of a supraspinatus muscle) may be present In the absence of roentgen-ray alterations diagnosis rests on clinical findings swelling, tenderness, painful limited motion

A "temporo-mandibular joint syndrome," described by Costen^{7,8,9} may arise from mal-occlusion of natural or artificial teeth or in edentulous mouths Mandibular joint destruction may result from lack of molar teeth or badly fitting dental plates permitting overbite articular destruction may be unilateral from one-sided, poor molar support Symptoms are variable and include constant or intermittent catarrhal deafness, "stuffiness" of ears, tinnitus, snapping noises in ears while chewing, dull pain in and about ears with or without herpes of the external canal and buccal mucosa, dizziness (generally mild, sometimes severe), severe constant headaches which may be vertical, occipital or postauricular and which persist after "sinusitis" is treated, glossodynia or burning pain in the throat or side of nose, and tenderness over mandibular joints Symptoms may be promptly relieved by inflating eustachian tubes or interposing disks between the jaws Roentgenograms may show erosion of heads of condyles and articular eminences Symptoms are produced by erosion of the bone of the glenoid or mandibular fossa, impaction of condyles against the thin bone separating them from the dura and its rich nerve supply, irritation of the auriculotemporal nerve, reflex pain and sensory disturbances in the chorda tympani nerve Treatment consists of repositioning the jaws by proper dentures which move condyles away from the range of the chorda tympani and auriculotemporal nerves

(No description of the micropathology of joints was given—Ed)

Articular Disease Aggravated by Trauma If an injured patient is found to have had previous symptoms in other joints, a mild atrophic arthritis may be present (Bick⁶) The assessment of disability is difficult for patients who after injury are found to have hypertrophic changes in the

spine, hips or knees These changes may have long antedated the injury and may represent, not traumatic hypertrophic arthritis, but senescent hypertrophic arthritis which is so common in men over 40 years of age and which may be symptomless Such a condition may be aggravated or made symptomatic by injury The effect of injury can be evaluated only by noting the degree of greater functional and roentgenographic abnormality on the injured side than on the opposite side affected only by senescent hypertrophic arthritis

Pathologic and Roentgenographic Alterations According to Bick,⁶ the primary reaction in traumatic arthritis is invariably synovitis, "a congestion of synovial and subsynovial strata" Allison and Ghormley (1931) showed that when cartilage is affected, a degenerative arthritis may be produced fibrillation and degeneration of cartilage Secondary reactions in articular bone may occur, producing roentgenographic changes hypertrophic in nature Roentgenographic alterations in traumatic hypertrophic arthritis therefore may resemble those in senescent hypertrophic (osteo-) arthritis That two such widely different causes (acute trauma on one hand, and presumably a chronic degenerative process of age and wear and tear on the other) may produce similar roentgenographic abnormalities indicated to McMurray¹⁰ that "hypertrophic arthritis" (in the roentgenographic sense) is not one disease but a reaction of articular tissues to several different agents (including gout and gonorrhea—Ed) It must be borne in mind, then, that roentgenographic "hypertrophic arthritis" is not necessarily either traumatic hypertrophic arthritis or senescent hypertrophic (osteo-) arthritis McMurray¹⁰ and Doub¹¹ believed that monarticular hypertrophic arthritis, particularly of a hip, probably represents traumatic hypertrophic arthritis, but bilateral hypertrophic arthritis represents the syndrome of senescent hypertrophic (degenerative, osteo-) arthritis

Doub and Jones¹² were unable to prove that single, severe trauma produced hypertrophic arthritis Thirty patients, aged 12 to 71 years (average 44), suffered fracture of one of the long bones of a leg Eight months after injury there was no evidence of arthritis of adjacent hips or knees in 28 cases In one case moderate hypertrophic arthritis of a knee, present before injury, was not increased In one case of fracture of the upper part of a femur, which united strongly but with a definite varus deformity, slight changes indicating an early arthritis of the adjacent knee resulted It was concluded that chronic trauma was a much more likely factor than single acute trauma in producing hypertrophic arthritis

Synovial Fluid in Traumatic Arthritis Synovial fluid in traumatic arthritis may be characteristically altered increased erythrocyte content and icteric index (Forkner, 1930) The finding of a positive Wassermann reaction on synovial fluid should not necessarily change the diagnosis from traumatic to syphilitic arthritis Bick⁶ reminds us of Osler's dictum "Even a syphilitic may have traumatic arthritis"

Treatment Early vigorous treatment of injured joints may be necessary to prevent chronic disability^{13, 14} This includes rest and the proper type of physical therapy In some cases physical therapy may give great relief, in others (post-traumatic epicondylitis humeri) rest and splints alone may be indicated Physical therapy should not be long continued when no benefits are derived therefrom By treating compensation cases too long physicians may make invalids of them, taking from them the responsibility of getting well and making them rely on somebody else In such cases physical therapy should be given in a hospital by a physician on a fixed salary, independent in his judgment as to when a patient should be discharged Professional physical therapy should be supplemented by home physical therapy

Carruthers¹⁵ reported that early aspiration of synovial exudates in knees was generally followed by early resumption of walking and a good functional restitution He favored avoidance of weight bearing for a week after aspiration, advising the patient to move his joint in bed, and allowing him to walk with crutches Bick⁶ condemned the routine aspiration of such exudates unless they are persistent

By applying a "sponge-compression dressing" Forrester¹⁶ avoided the use of aspiration, casts or splints in cases of traumatic synovitis of knees

A protective cotton pad was placed in the popliteal space and held in place by a circular dressing of sheet wadding A porous rubber bath sponge was cut longitudinally to fit the contour of the synovial cavity This was held in place by a gauze bandage By its gradual expansion as the exudate resorbs, the rubber sponge exerts a constant compression which hastens absorption of the exudate The bandage is reapplied every four or five days The exudate disappears in three to six weeks No edema of the leg occurs and the patient is permitted to walk and work throughout treatment

Histamine iontophoresis was advocated by Kling¹⁷ The use of short wave or high frequency diathermy was favored by Bierman and Schwarzschild¹⁸ Synovectomy¹⁹ and arthroplasty^{20, 21} are occasionally indicated

Stenosing Tendovaginitis at the Radial Styloid Since its first description in 1895 by de Quervain, about 200 cases of this condition have been reported The tendon sheaths of the abductor longus pollicis and extensor pollicis brevis are involved in a marked fibrosis of the common sheath in the groove at the lower end of the lateral surface of the radius Brown²² recorded a typical case, the third report in English The condition is regarded of traumatic origin from excessive use of the thumb as in writing, washing, wringing clothes, chopping wood, and so forth

Brown's patient, a woman aged 62, had a severe constant boring pain in the left wrist at the styloid process Pain invaded the arm and was aggravated by motion of the wrist, especially of the thumb Local swelling and tenderness were present Although roentgenograms are usually negative, periostitis was present De Quervain's operation is generally advocated for such conditions incising the tendon sheath under local anesthesia Operation being refused in this case, a plaster

cast was applied to the wrist and thumb, the latter in full abduction and extension. After 18 weeks the patient was cured. (It is regretted that the diagnosis of stenosing tendovaginitis rather than local periostitis could not have been verified by operation—Ed.)

GONORRHEAL ARTHRITIS AND TENOSYNOVITIS

Clinical Data The clinical features of gonorrhea of articular and periarticular tissues have again been reported^{23, 24, 25}. To his previous series of 69 cases presented with Keefer,² Myers has added 16 more, reported with Gwynn.²⁵ Several points are worthy of reemphasis. Gonorrheal arthritis generally appears within 10 to 21 days after the initial urethral infection, but occasionally may not appear for months or years thereafter. An acute polyarthritis or polyarthralgia was present in 87 per cent of the cases of Myers and Gwynn. An initial polyarthralgia may resolve into a more stubborn monoarthritis. A monoarthritis alone was present in only 13 per cent of the cases. This is contrary to previous teaching. Knees, ankles, wrists, metacarpophalangeal joints and shoulders are most frequently affected. Fever (to 104° F) and leukocytosis (to 23,000 leukocytes) are generally present. The sedimentation rate was increased in all of Myers and Gwynn's cases. Certain misconceptions have been that gonorrhea affects the os calcis with spur formation so often that most cases of calcaneal spurs should be considered gonorrheal, and that involvement of the spine, temporo-mandibular or sternoclavicular joints is common. Current reports again refute these ideas. Gonorrheal spondylitis is uncommon. Of Woods' ²³ 70 patients with gonorrheal arthritis, only one had spondylitis. Involvement of a sternoclavicular joint is "unusual"²³, only two of 85 patients had it.²⁵ Gonorrheal spurs are rare—seven instances in 85 cases. These observations confirm Von Lackum's contention (1930) that "gonorrheal spurs" is a misnomer.

Gonorrhea tends to affect tendon sheaths. Tenosynovitis with arthritis is common. Extensor tendon sheaths of palm and wrist are most commonly affected. Of Myers and Gwynn's ²⁵ patients with gonorrheal arthritis, 48 per cent had tenosynovitis. It occurs without arthritis much less commonly. The incidence of purulent tenosynovitis is reputedly rare—1 in 7,000 cases of gonorrhea in males. Four new cases were reported by Murray and Morgan,²⁶ Zadek,²⁷ and Birnbaum and Callander.²⁸ The last named reviewed the literature. The tenosynovitis may be acute or chronic. Although severely affected, the tendons are rarely destroyed. Mild subacute trauma precipitated, and conditioned the location of, the attacks in three of the four new cases reported. Involved areas were the long head of the biceps brachii at the left shoulder, the radial and ulnar bursae at a wrist, and the tendons of a right thumb and those of an index finger. Gonococci were found in smears of pus from two of three cases examined. In Zadek's case, smears and cultures from pus were negative for gonococci, but microscopic examination of the tendon sheaths showed numerous pus cells with intracellular, gram-negative, biscuit-shaped diplococci.

(The patient denied genital gonorrhea. A purulent vaginal discharge was present but smears revealed no gonococci. Gonococcal complement fixation test was negative on the third day of the tenosynovitis. Regardless of these facts the report and photograph seem to warrant acceptance of the diagnosis made—Ed.)

Surgical drainage was performed in these cases. Functional restitution was generally good.

Complications In 20 per cent of Myers and Gwynn's cases²⁵ a catarrhal conjunctivitis was present. Non-purulent in type, it lasted about two weeks. No gonococci were recovered from the scanty mucoid exudate. Iritis was present in 3.5 per cent, ulcerative aortic endocarditis in 2.4 per cent. Woods²³ occasionally noted lymphangitis.

Roentgenograms Some have asserted that roentgenographic alterations in gonorrheal arthritis are at times highly characteristic if not pathognomonic. Ankylosis between patella and femur, "moth eaten vacuolated areas of decalcification," and "spotty ground-glass atrophy" of juxta-articular bone have been offered as characteristic alterations. The majority opinion has been that such alterations simulated those of other arthritides and were not specific. This was the conclusion of Kapo²⁴ and of Ferguson, Kasabach and Taylor²⁰. A great variety of nonspecific alterations, from simple soft-tissue swelling to diffuse bony ankylosis, was encountered, as should be expected in a disease of such diverse manifestations and variable severity. A clinical diagnosis cannot be ventured by a roentgenologist unless he knows the approximate duration of an arthritis and whether the part has been used. In some cases of acute gonorrheal arthritis of short duration, roentgenograms may resemble those of old tuberculous arthritis. If one is familiar with the time elements in a given case, when a roentgenogram exhibits destructive changes simulating tuberculous arthritis which are known to have developed rapidly (within a few weeks—much faster than is usual in tuberculous arthritis)—such a roentgenogram should arouse suspicions of gonorrhea. Diagnosis must be confirmed by clinical data.

Laboratory Data Diagnosis and proper treatment of gonorrheal arthritis depend of course on proof that the patient has gonorrhea. It is imperative that physicians be familiar with certain special knowledge: the rather individualized technic of obtaining an honest history, the physical signs to search for and the best method of examination, and the relative significance and reliability of clinical and laboratory data. These matters are reviewed in further papers³⁰ of the Neisserian Medical Society of Massachusetts.

Isolation of Gonococci Isolation and identification of gonococci from smears are less accurate than by the new culture method which utilizes "the oxydase reaction" with tetramethylparaphenylenediamine hydrochloride, bacterial growth being enhanced by an atmosphere of CO₂. First described by Gordan and McLeod (1928), the method was modified and extended by McLeod and his associates (1929, 1934). Its value was confirmed by Price (1929) and by Leahy and Carpenter³¹. Thompson³² simplified the

manner of applying CO₂. By this method gonococci were isolated by McLeod et al (1934)² twice as often as from smears

(One of us noted the comparable recovery of gonococci by the two methods as done by Thompson. From 175 patients suspected of having gonorrhea, cultures or smears were "positive" in 44 [25 per cent]. In 14 of these 44 cases both cultures and smears were positive, in 30 cases smears were negative but cultures were positive. Cultures have been of great help in confirming suspicions of gonorrheal arthritis.—Ed.)

When synovial exudates were present, gonococci were recovered by Myers and Gwynn²⁵ from 25 per cent of the exudates. Kinsella³³ found it extremely difficult to recover gonococci from synovial fluid in cases with a copious, thin straw-colored effusion, but found them with comparative ease both in smears and on culture in cases presenting a dense, brawny, exquisitely tender periarticular infiltration and relatively scanty purulent synovial fluid.

Gonococcal Complement-Fixation Reaction This test on blood is gaining recognition as one of considerable value, one that should become a routine diagnostic procedure^{29, 34}. King³⁵ feels it is as useful in gonorrhea as the Wassermann reaction in syphilis. Myers and Gwynn²⁵ found it positive in 86 per cent of 43 cases of proved gonorrheal arthritis. McEwen, Bunim and Alexander²⁹ obtained a positive reaction in 98 per cent of 43 cases. Certain errors in technic and in the interpretation of the test must be avoided. By using a new antigen and a new technic, Price³⁶ thought the test had been made more dependable and cross-fixation reactions had been excluded. By testing complement both for its hemolytic and fixing powers, irregularities can be avoided, according to Thomson, Hamann and Park.³⁷

The reaction is usually negative, rarely positive the first 10 days, and generally becomes positive between the second and third week of infection. A negative reaction may sometimes be obtained if a urethral infection is "open" such a negative test indicates efficient drainage with insufficient absorption of substances to produce the reaction in blood. In such cases a negative test can and does occur even when smears are positive (King³⁵). A negative test should also be expected when a patient with gonorrhea is really cured or in non-gonorrheal cases. A weakly-positive reaction should not be considered certain evidence of infection, but if it is repeatedly (weakly?—Ed.) positive or strongly-positive Price³⁶ concludes that the patient has gonorrhea. Repeated tests are recommended and will prevent diagnostic errors. Tests should always be interpreted in the light of clinical findings. Special caution must be taken to avoid errors in diagnosis when a patient with old or recent gonorrheal urethritis later develops a (coincident) non-gonorrheal arthritis. A positive complement fixation reaction may be present but is unrelated to the arthritis^{23, 29}.

Skin Reactions to Gonococcus Filtrate When Cumming and Bur-

hans³⁸ gave intradermal injections of gonococcus filtrate (Corbus-Ferry) in the treatment of gonorrhea, the urethral discharge at times increased, as it may with nonspecific protein injections. Local skin reactions at the site of injection included an area of redness surrounding a wheal. Injections of 0.1 to 0.4 c.c. of the filtrate into non-gonorrheal controls produced no skin reaction and no urethral discharge. Cumming and Burhans concluded that both the provocative effect on the discharge and particularly the skin reaction are useful in diagnosis. They thought that the skin reaction was specific because injections of bouillon used in preparation of the filtrate produced no reactions in gonorrheal or other patients.

(The report presents but few details of the reaction. "Several" controls were used. Further information should be forthcoming before one can evaluate the procedure.—Ed.)

Differential Diagnosis When, as often happens, gonorrheal arthritis begins as an acute polyarthritis or polyarthralgia, shifting rapidly from joint to joint before localizing (if ever) more stubbornly in one joint, its differentiation from rheumatic fever may be difficult as two of Myers' cases illustrate.³⁹

A young woman developed acute febrile polyarthritis. Aside from her joints, physical examination was negative. A diagnosis of rheumatic fever was entertained, but salicylates persistently failed to give relief and electrocardiograms were repeatedly normal. Dissatisfied with a diagnosis of rheumatic fever, Myers examined synovial exudate. Gonococci in pure culture were found. The synovial leukocyte count was 58,900 (90 per cent being polymorphonuclear cells). The gonococcal complement fixation test was positive on blood and on synovial fluid. Uterine cervical secretions revealed no gonococci.

A young man developed an acute, febrile migratory polyarthritis five days after an upper respiratory tract infection. The heart was not enlarged. An apical systolic murmur was present, transmitted to the axilla. The second pulmonic sound was accentuated. He had had gonorrhea four and seven years previously and prostatic secretions now contained gonococci. Gonorrheal polyarthritis was considered, but the electrocardiogram revealed partial heart block, a PR-interval of 0.24 second. Aspirated synovial fluid contained 10,450 leukocytes per cu. mm., 88 per cent being polymorphonuclear cells. No gonococci were found in the synovial fluid and the gonococcal complement fixation test was doubtfully positive thereon and on blood. When salicylates were given the fever and arthritis subsided but returned when salicylates were omitted. A presystolic murmur developed. Final diagnosis was rheumatic fever, with rheumatic polyarthritis and carditis and an incidental prostatic gonorrhea.

In the differentiation of gonorrheal polyarthritis and rheumatic fever, these points are important. The value of the complement fixation test and diagnostic aspiration of synovial fluid is evident but results must be carefully interpreted. Prodromal pharyngitis commonly initiates rheumatic fever but is not infrequently seen with gonorrheal arthritis (10 per cent of Myers' 69 cases). Electrocardiographic alterations speak for rheumatic fever, as do response to salicylates and associated involvement of pleura or

lungs The presence of serous conjunctivitis suggests gonorrhea (it was present in 20 per cent of Myers' cases)

Treatment Further experience indicates that fever therapy may be the method of choice For patients for whom fever therapy is not available or is contraindicated other methods must be used Garland's experience⁴⁰ with roentgen therapy in 30 cases of gonorrheal arthritis led him to believe it may be equal or superior to fever therapy Roentgen therapy is much simpler than fever therapy, which he considers an exhausting "ordeal by fire" Affected joints were given small doses of roentgen-rays twice weekly for two to three weeks Some patients had previously had foreign protein therapy without relief Twenty-eight patients (93 per cent) were much improved, two (7 per cent) were unimproved A total of 80 joints were affected 30 became symptom free, 45 were "improved," five were unimproved About 50 per cent of the improved cases appeared to be completely cured within a few weeks after treatment (This apparently refers to articular lesions no comments on the primary infection were made) The remainder improved gradually, became free of pain but had slight articular stiffness or disability Five patients, certain of whose joints were left untreated as controls, showed no improvement in untreated joints Garland cited the similar experiences of Akerlund (1930) and of Westermarck (1933) the former regarded the effect of roentgen therapy in gonorrheal arthritis as "magical," the latter as better than any other method for gonorrheal hips

(Garland's report is arresting both because of, and in spite of, its optimism The matter of controls might seem to have been satisfied by the continuation of disease in untreated joints, but this is not full proof Garland realized that gonorrheal arthritis is an extremely "labile" form of arthritis, often capable of being rapidly relieved by various remedies or spontaneously by the self-limiting nature of the disease His comment that in some of the acute cases the relief of pain was "almost theatrical" makes us believe that a transitory arthralgia, not a true arthritis, must have been frequently present No adequate explanation of the relief is offered, no cultural examination of joints was made, no study of the effects of roentgen-rays on the gonococcus in vitro or in vivo It is to be regretted that results in this series were not compared with a control series of patients whose joints were treated otherwise, or were untreated—Ed)

Three patients "were benefited" with histamine iontophoresis (Kling¹⁷) Cases of gonorrheal arthritis were among the arthritides that responded favorably to gold salts (Forestier,⁴¹ Slot⁴²)

(In these reports few or no details concerning the joints are given, the number of patients treated is quite small and no control series treated by other than the favored remedy is presented—Ed)

Gonococcal immunogens, sterile milk, lactalbumin and the intradermal use of stock gonococcal vaccines are valueless according to Cumming and Burhans³⁸, but the use of gonococcus filtrate (Corbus-Ferry) seemed to give "specific aid" in the treatment of 124 patients with gonorrhea and its

complications, including arthritis. This filtrate is a soluble toxin and is not to be confused with vaccines (bacterial suspensions), immunogens (bacterial washings), toxoids (solution of formaldehyde detoxified toxin) or serums (antitoxins). Patients generally received 7 to 10 injections, sometimes as the sole treatment, usually as an "adjunct to mild local treatment."

(Results were not statistically presented, no controls were mentioned. Hence evaluation thereof is not possible—Ed.)

Wolbarst⁴³ considered gonorrheal arthritis usually secondary to a primary focus in the vesicles for which vasotomy, with the injection of 5 per cent argyrol, is the most effective treatment. In such cases Goldstein,⁴⁴ however, opened the vesicles and drained them by perineal exposure. When aspiration of joints revealed serous or serofibrinous synovial exudate, Cooperman¹⁹ used "closed drainage" (aspiration and irrigation). When thick turbid exudate was recovered, "open drainage" by incision was necessary to prevent serious articular destruction. (Some of us believe that even in such cases conservative treatment, aspiration and rest, or fever therapy, is effective—Ed.) By one or the other method Wolbarst⁴³ treated 136 gonorrheal joints of 43 infants, to all but 11 joints complete functional restitution was provided. After ankylosis has occurred much can still be done by arthroplasty^{20, 21}. To prevent articular and other complications, in view of the local influence of trauma, Woods²³ advised patients with acute gonorrhea to live a sheltered life, preferably in bed temporarily.

Fever Therapy. Sixteen more reports on fever therapy for gonorrheal arthritis have appeared since those mentioned in our last Review (Warren, Carpenter, Boak⁴⁰, Kendell, Webb, Simpson^{45, 46}, Tenney⁴⁵, Atsatt and Patterson^{45, 47}, Hench, Slocumb and Popp^{45, 48, 49}, Bierman, Horowitz^{45, 50}, Stecker⁴⁵, Hefke^{40, 51}, Arnold⁴⁵, Lepore⁴⁵, Schnable and Fetter^{45, 52}, Strickler^{45, 53}, Short and Bauer⁵⁴, Wolf⁵⁵). (One of us has published summaries of the literature on this subject to date [Hench^{29, 48, 56}—Ed.]) Current reports apparently confirm the excellent results noted earlier. It would appear that fever therapy acts almost as a "specific" in the majority of cases of gonorrhea and its complications. Some regard the development of fever therapy for gonorrheal arthritis as the greatest advance of the decade in the field of articular diseases. Therefore, a brief tabular synopsis of reports published from 1932 to 1935, inclusive, seems worthy of presentation (table 1).

Boak, Carpenter and Warren⁴⁵ showed that the thermal death time of 130 strains of gonococci in vitro at 106° to 107° F. was about 6 to 27 hours. A patient may be infected with more than one strain. Strains derived from a patient and from his consort generally have the same thermal death time. When a patient exhibits strains whose thermal death times differ markedly, he is probably affected with both an old and new infection. Articular strains are somewhat less resistant to heat than urethral strains, therefore, gonorrheal arthritis may subside before an associated urethritis does.

TABLE I
Results of Fever Therapy for Gonorrheal Arthritis (1932 to 1935)

Authors	Method used	Dose of fever		Treatments		Number patients treated	Results per cent				Comments
		Hours each treatment	Temperature (Fahrenheit)	Days interval	Total number		"Cured," Symptom-free	Marked relief	Mod-erate relief	Little or no relief	
Carpenter and Warren (1932)	Diathermy and radiothermy	5-7	106.7	*	1-2	*	*	*	*	*	"Gonorrheal arthritis usually cured"
Bishop Horton and Warren (1932)	Diathermy and heated cabinet	5	106.7-107 (rectal)	*	2	9	*	*	*	*	Results very encouraging joints become painless
Warren and Wilson (1932)	*	5	106.7 (rectal)	*	1-2	2	100				
Warren, Carpenter, and Boak (1935) ⁴⁵	*	5-17	106.7 (rectal)	*	1 (equal to thermal death time of patients strain)	15	87	*	*	*	"Patient may be infected with two strains. The thermal death time of that of patient and consort generally about the same. Strains from urethra and joints may have different thermal death times, usually a little shorter from joints"
Tenney (1932)	Radiothermy	3-4	101-106 (rectal)	*	*	*	*	*	*	*	"Acts almost as a specific"
Tenney (1935) ⁴⁵	*	*	*	*	*	3	100				
Berris (1933)	Heated cabinet	2-4	102-103	*	1-6	2	50			50	
Simpson Kiebig, and Sittler (1933)	Radiothermy and heated cabinet	5	105-106 (rectal)	*	*	*	*	*	*	*	"Results gratifying"
Simpson (1934)	Radiothermy and heated cabinet	5	105-106.8 (rectal)	7	*	12	100				"Results uniformly successful in acute cases"
Kendall Webb and Simpson (1935) ⁴⁶	Kettering hypertherm	6-7	106-107	3-5	1-5	Acute 19 Chronic 12	84 11	*	*	*	

TABLE I—Continued

Authors	Method used	Dosage of fever		Treatments		Number patients treated	Results per cent				Comments
		Hours each treatment	Temperature (Fahrenheit)	Days interval	Total number		Cured Symptom free	Marked relief	Mod-erate relief	Little or no relief	
Atsatt and Patterson (1933)	Diathermy and heated cabinet	2-6	103.5 (oral)	*	*	Acute 8	88		12		In failure temperature given was too low
Atsatt and Patterson (1935) ^{45 47}	Diathermy and hot air cabinet	2-4	104-105	7	1-5	Chronic 1	100				
Kovacs and Kovacs (1933)	*	*	*	*	*	*	*	*	*	*	Good results even in stubborn chronic gonorrheal arthritis
Hedrick (1933)	*	*	*	*	*	Acute 1		100			
Jones (1934)	*	*	*	*	*	Acute 10	100				
Hench, Slocumb and Popp (1935) ^{48 49}	Kettering hypertherm	5	106-106.8 (rectal)	3-4	3-6	Acute 9 Chronic 7	44 14	56 58	14	14	
Hench (1935) ⁴⁹	Kettering hypertherm	5	106-106.8 (rectal)	3-4		Acute 1	100				Combined general and local heat (pelvic diathermy electrode)
Bierman and Horowitz (1935) ^{45 50}	General fever Phototherapy cabinet Local pelvic diathermy electrode	3-4	105-106 (rectal) 111-112 (pelvic)	14	3	2	100				Complete cure if bony changes not present Physiotherapy for residual stiffness
Bierman (1935) ^{45 50}	General fever Phototherapy cabinet Local pelvic diathermy electrode	3-4	105-106 (rectal) 111-112 (pelvic)	11	3	16	81		6	13	
Steecker (1935) ⁴⁵	*	*	106	*	1-2+	18	61		33	6	
Hefke (1935) ^{45 51}	Kettering hypertherm	5-6	105-106	*	3	4	100				

TABLE I—Continued

Authors	Method used	Dosage of fever		Treatments		Number patients treated	Results per cent				Comments
		Hours each treatment	Temperature (Fahrenheit)	Days interval	Total number		Cured Symptom-free	Marked relief	Mod-erate relief	Little or no relief	
Arnold (1935) ⁴⁵	*	*	*	*	*	19	89	11			Results remarkable
Lepore (1935) ⁴⁶	*	*	106-107	*	*	6	100				
Selnable and Fetter (1935) ⁴⁷	Kettering hypertherm	5	106-107 (rectal)	7	2-6	Acute 9 Chronic 9	67 56	22 33	11 11		In acute cases results striking, to miraculous
Strickler (1935) ⁴⁸	*	6-7	105-107	*	4	Acute 9 Chronic 4	15	22	22 75	11 25	No better than other treatment
Short and Bauer (1935) ⁴⁹	Diathermy	*	*	*	*	*	*	*	*	*	Nearest thing to specific ever employed. Results remarkable but equally favorable results from fever reactions to typhoid vaccine given intravenously
Wolf (1935) ⁵⁰	*	*	*	*	*	*	100				'Acute cases all cured'
<i>a</i> Estimated total (not recounting overlapping series) acute and chronic											
<i>b</i> Estimated total of cases presumably acute (those not listed as chronic)											
<i>c</i> Total cases known to have been acute (definitely stated)											
<i>d</i> Total chronic cases (more than six weeks duration)											
						182†	About 70	About 15	About 10	About 5	
						149‡	About 75	About 10	About 10	About 5	
						66	About 70	About 15	About 10	About 5	
						33	About 30	About 45	About 15	About 10	

* Incomplete data
† $b + d = a$
‡ b includes c

When estimations of the thermal death time are possible, applications of a single session of fever, of a number of hours equal to the thermal death time (generally 5 to 17) at 106° to 107° F, were advocated recently by Warren, Carpenter and Boak⁴⁰ Prompt cure was practically always obtained for those so treated Good results were also obtained, however, when a period of fever of three-fourths to half the thermal death time was given, suggesting the assistance of defense factors in the body Since routine estimation of the thermal death time of a patient's strain is not yet practicable, most physicians favor a number of short sessions (as table 1 shows) rather than one long session, but sessions should be given not less than twice a week or strains may become heat resistant

Various methods for producing artificial fever have included general diathermy, general (as contrasted with local) radiothermy, heated air-conditioned cabinets, hot baths and heated air currents An analysis of results does not suggest that one is superior to another so far as they affect the disease A choice of method resolves itself into selection of that one which is most comfortable, least dangerous and least expensive to the patient The majority favor the administration of 5 to 6 hours at 106° to 106.8° F (rectal) as one session Treatments are given every 3 to 5 days Two to five or six fever sessions are necessary, generally fewer for acute than for chronic gonorrheal arthritis Statistical data permitted the percentage evaluation of published results in a total of 182 cases of acute and chronic gonorrheal arthritis Of these 182 patients, 70 per cent (128) were more or less promptly "cured," becoming symptom-free About 15 per cent more were markedly relieved, about 10 per cent were moderately relieved, and 5 per cent received little or no benefit Results were definitely better in acute than in chronic cases (over 6 weeks' duration) Of a total of 33 patients with chronic gonorrheal arthritis, about 30 per cent were "cured," about 45 per cent markedly relieved, 15 per cent were only moderately relieved and about 10 per cent were not benefited Considering the remaining 149 patients to have had acute arthritis, about 75 per cent were "cured," 10 per cent markedly relieved, 10 per cent only moderately relieved and 5 per cent unrelieved If one chooses to consider as acute only the 66 specifically labelled as "acute cases," the results were still most gratifying and were about the same 70 per cent were cured, 15 per cent markedly relieved

Of the approximately 30 reports to date only one is at variance with the others In Strickler's experience^{45, 53} results in 13 cases were no better than with other treatments, nevertheless in his 9 acute cases, 6 patients were cured or markedly relieved Short and Bauer⁵⁴ obtained "excellent results" with artificial (diathermy) fever but obtained equally good results with fever induced by typhoid vaccine intravenously

(Culver in 1919 noted marked improvement in 22 of 24 patients with gonorrhea treated by fever from intravenous injections of killed colon bacilli, meningococci or gonococci—Ed)

These experiences indicate that in cases of gonorrheal arthritis some form of fever therapy should, when possible, be instituted early, but the method used must be able to provide a controllable fever sufficient to reach or exceed the thermal death time of the gonococcus. In cases in which gonorrhea is strongly suspected but cannot be proved, the patient should always be given the benefit of the doubt and be subjected to a couple of trial sessions of fever. If his response is marked, gonorrhea probably was present. Patients who have had arthritis more than six weeks have lost valuable time, but even in chronic cases results may be quite good. However, fever therapy should be regarded as a fire-brigade, not a corps of carpenters, it may extinguish the flames of gonorrhea but will not restore the architecture of the joint. Therefore, when a process is almost burned out except for residual stiffness, fever therapy is not indicated. In two cases of chronic gonorrheal arthritis seen by Kendell, Webb and Simpson,⁴⁶ marked stiffness remained after fever therapy alone, but this was relieved by orthopedic manipulation under anesthesia immediately followed by a fever session.

Gonorrhea of the female pelvis is more difficult to cure than this same infection in males. In such cases the combined use of fever therapy and Elliott treatments or pelvic diathermy may be more effective than fever therapy alone (Simpson⁴⁵). Bierman and Horowitz^{45, 50} strongly favored the supplemental use of vaginal diathermy electrodes as productive of more local heat than Elliott treatments. Treated by a general temperature of 105° F by fever cabinet and a vaginal temperature of (not more than) 110° to 111° F by vaginal diathermy, 37 of 41 patients became bacteriologically "negative" after one to three sessions.

Criteria of Cure The patient considers his joints cured when symptoms leave, the patient himself is not well until the original focus is also cured. Of 29 patients treated by Desjardins, Stuhler and Popp,⁵⁷ 25 were cured after one to 10 fever sessions, "cure" meaning complete disappearance of urethral discharge, symptoms and gonococci in spite of repeated smears and culture, patients remaining free of symptoms for several months. Discharges ceased and smears became "negative" in 9 cases after one fever session, in four cases after two sessions, in three cases after three sessions, in two cases after four sessions and in four cases after five sessions. Three were cured only after seven, eight and ten sessions. King's³⁵ criteria of cure were essentially similar although he relied considerably on the complement fixation test. In cases wherein treatment was by gonococcus vaccine the test became negative six weeks after patients were clinically cured. However, a negative test is less reliable than a positive test. King believed that when a patient not treated with gonococcus vaccine still presents a positive test even in the absence of symptoms, a persistent focus of infection is undoubtedly present.

(None of these reports included control series of patients treated other than by fever. It cannot be doubted that results from fever are excellent, but fever therapy is a strenuous, expensive, and difficult form of therapy to apply, one which probably

should not become routine in all cases. There are certain dangers in and contraindications to fever therapy. One must remember that articular gonorrhea disappears rapidly and spontaneously in many cases, particularly if "arthralgia" and not true arthritis is present. Even so, under older methods of treatment many cases responded satisfactorily without residue, generally those with serous and not purulent synovial exudate with involvement mainly in subsynovial rather than synovial tissues,—cases in which the synovial cavity was probably not actually invaded by gonococci (Myers, 1934). Statistics on end-results of older methods are, curiously, difficult to find. Only a few are cited in Mondor's extensive monograph⁵⁸. Complete restitution of articular function was obtained in 50 per cent of Rasch's cases (1916), in 61 per cent of Schussler's cases (1912). Others noted serious sequelae and articular impotence in at least 30 to 50 per cent of cases (Charrin, 1914). In only 30 per cent of Kong's and in only 14 per cent of Bodganow's cases (1904), were joints completely cured. Results by older methods depended, of course, on the degree of articular involvement—whether purulent arthritis, or merely a toxic arthralgia or non-purulent arthritis, was present. Further data on how many cases of each type become healed spontaneously, and how many with treatment recover with or without residue are needed as controls to fever therapy. A more rigid evaluation of fever therapy would be obtained by selecting for treatment only those with positive synovial cultures. However, faced with a method which seems to insure the prevention of complications and a rapid (if strenuous) cure in the great majority of cases of urethral gonorrhea, and early restitution of function in those with arthritis, the matter of selection becomes difficult, and one hesitates to set up controls treated by methods which now seem outmoded. Results in cases of patients so treated, patients unable to afford fever therapy or for whom it is contraindicated, should be carefully compared to those herein tabulated—(Ed.)

General Remarks on Fever Therapy Fever therapy should not be given in a physician's office. It can be safely administered only in a hospital equipped with specially trained personnel. However, hospitalization after each fever session is generally unnecessary. Physiologic studies have shown that the amounts of fever usually prescribed generally do not harm patients. Hundreds of patients with a variety of diseases have now been so treated. In one series of 400 patients no untoward reactions occurred (Simpson⁴⁵). However, an occasional serious and even fatal reaction is probably inevitable. Only a very few deaths from uncontrolled hyperpyrexia have been reported, four occurred recently of whom two were patients being treated for gonorrhea, one of whom had gonorrheal arthritis^{45, 59, 60}. The great majority of patients tolerate the fever quite well but, to prevent such mishaps, physicians and technicians must be familiar with the physiologic reactions to fever therapy, contraindications, management of patients during sessions, and signs of impending trouble as discussed in the references already mentioned. Interesting also are the following references on physiologic reactions to fever therapy^{45, 61, 62, 63, 64, 65}, on immunologic reactions^{66, 67}, on various methods used for the production of fever^{68, 69, 70}, and on its clinical application and the management of patients^{71, 72, 73, 74, 75, 76}.

Short-Wave Therapy This should not be confused with "fever therapy". In the early development of fever therapy short waves were used to produce the fever by "general radiothermy" or "general short-wave dia-

thermy" Patients received a general, not a local application of the waves Now, short wave currents are being used to produce merely a local heating or other local effect, not a general fever In this newer utilization of short waves only local parts, such as joints, are exposed to the waves

The method is variously called "short-wave" (or "ultra short wave") therapy or "short wave high-frequency" (Schliephake) or "short wave diathermy" (Nagelschmidt), "radiothermy" (Bierman) or "radiathermy" (Kobak) Ordinary or "long-wave" diathermy concerns a wave length of 100 to 400 meters (a current frequency of $\frac{1}{4}$ to 3 million cycles per second) "Short wave diathermy" (the term approved by the Council on Physical Therapy of the American Medical Association) concerns a wave length of 12 to 30 meters (10 to 25 million cycles per second) "Ultra-short wave diathermy" concerns a wave length of 3 to 12 meters (up to 100 million cycles per second) With ordinary diathermy, heat is produced by conduction, with short wave diathermy heating is due to dielectric losses in a condenser field⁷⁷

Patients with gonorrheal arthritis were benefited by short wave currents, according to Bierman and Schwarzschild,¹⁸ Kling,⁷⁸ Torbett,⁷⁹ and Kobak⁸⁰ Kling found reports of 25 patients so treated, with "improvement" in 23 Two of his own patients treated by a 23 meter wave machine also "improved" Of six patients treated by Torbett, 3 obtained "good improvement", 3 were "moderately improved" One of Kobak's patients with a gonorrheal wrist obtained marked relief from three treatments

(No details were given in any of these cases—Ed)

Several special claims are made for short wave therapy, among them greater and more uniform penetration of heat into the body With ordinary diathermy superficial tissues are heated more than deep tissues, with short wave currents this thermal gradient is presumably obliterated or reversed Some have been unable to demonstrate any greater or more uniform penetration of heat than with conventional diathermy^{81, 82} Others, inserting thermocouples into joints and other tissues of animals, observed greater internal (intra-articular) than surface temperatures⁸³ Other claims include a specific bactericidal action Foreign researches suggested that ultra high frequency currents have a lethal action on bacteria, not from a heating effect but because of the peculiarities of the frequency itself By a process called "point-heating" the temperature of microorganisms is presumably raised above their thermal death point without a corresponding elevation in the temperature of the medium^{84, 85} It is claimed that different bacteria are killed by different wave lengths These claims are contradicted, however, by several^{81, 86, 87, 88} Gonococci and other bacteria were unaffected by the various wave lengths used and "heatless bacteriolysis" was not noted

Before short-wave and ultra short-wave diathermy machines are used extensively, their construction must be improved, fire hazards lessened, and more data on their physiologic effects amassed⁷⁷ Using 14 different machines with varying wave lengths from 6 to 25 meters, Mortimer and Beard⁸² found no advantage of any one wave length over another for heating purposes

TUBERCULOUS ARTHRITIS

Clinical Data Among 12,386 admissions to one tuberculosis hospital were 500 patients with tuberculous arthritis, an incidence of 4 per cent⁸⁹ Joint tuberculosis rarely begins in the capsule Extension to joints occurs from an adjacent bone lesion Extension from small bones of the wrists or feet is rapid, that from large bones to adjacent joints may be very slow Weight-bearing joints are involved much oftener than others Joints of legs are affected about three times as often as those of arms (Meng and Chen⁹⁰) Of 224 affected joints in Cleveland's cases,⁸⁹ 95 per cent were in weight-bearing regions (spine included), only 5 per cent were of upper extremities In this series the order of involvement was spine, 49 per cent (especially seventh to twelfth thoracic), knees, 20 per cent, hips, 11 per cent, sacroiliacs, 7 per cent, tarsus, 6 per cent, ankles, 2 per cent, elbows, 2 per cent, wrists, 2 per cent, and shoulders or symphysis pubis, less than 1 per cent Tuberculosis of the sacroiliacs is particularly serious (Cleveland⁸⁹) It must be remembered that polyarticular tuberculosis is not uncommon An ankle, knee, elbow and the spine were affected in a case of Slocumb and Ghormley's⁹¹ Of 100 patients seen by Meng and Chen, 16 had two, four had three, and one had four regions affected Pulmonary tuberculosis has been reported present in from 6 to 65 per cent of cases of tuberculous arthritis In the series of Meng and Chen, 47 per cent had pulmonary tuberculosis, an additional 31 per cent had hilar tuberculosis Of Petter's⁹² 45 patients with tuberculosis of a knee, 82 per cent had tuberculosis elsewhere (55 per cent in the lungs) Tuberculous arthritis occasionally first appears after the age of 50 years Duncan⁹³ reported two cases in men, aged 67 and 68 years, respectively

Tuberculous cysts of the knee joint are rare Elliott⁹⁴ reported two cases with multiple cysts proved tuberculous at operation, roentgenographically they were indistinguishable from osteitis fibrosa cystica In a case of bilateral subdeltoid tuberculous bursitis, Deacon and Ghormley⁹⁵ excised bursae filled with rice bodies weighing 100 and 400 gm Preoperative palpation revealed a peculiar leathery crepitus considered of diagnostic importance

Roentgenograms "There exists no roentgen picture entirely typical of tuberculosis in any of its stages" (Sundt, 1931) To this remark Elliott⁹⁴ and Doub¹¹ agreed Minor variations previously reported² as being suggestive of tuberculosis were again noted by Doub Different roentgenographic aspects of tuberculosis of the knees were diagrammatically presented by Petter⁹²

Treatment The patient, not just his joint, is tuberculous and the patient's primary disease must be energetically treated Even at rest, patients may develop bacillemia with new articular and other foci⁹² The use of gold salts is "not quite so successful" in tuberculous arthritis as in tuberculous rheumatism, according to Forestier⁴¹ (No details were given—Ed)

The intra-articular temperature of a tuberculous joint can be elevated to 105° F by submersion baths⁹⁶ Fever therapy, however, is apparently of no value and may actually harm tuberculous patients Like physical exercise, fever therapy stimulates metabolism—an effect harmful in tuberculosis A few patients with tuberculous arthritis were treated and obtained no improvement therefrom (Duncan and Mariette,¹⁵ Hubei¹⁷) Temperatures available in fever therapy do not affect bovine or avian strains, and have no bactericidal but may have a bacteriostatic effect on human strains of *Mycobacterium tuberculosis* A patient with a tuberculous hip was unrelieved by short wave therapy⁷⁹

Results of conventional surgical treatment were reported^{15, 89, 97} When ankles were affected by abscesses and sinuses Cleveland⁸⁹ advised amputation He condemned resection of knee joints in childhood since it eventually produces considerable shortening of the leg The value of the usual orthopedic measures (resection, arthrodesis, osteotomy) has been questioned by Erlacher⁹⁸ Ankylosis is taken for granted as the ideal result Yet these common practices take years to complete, the tuberculous focus remains and recovery of normal joint function practically never occurs A purely synovial tuberculosis should be treated by synovectomy before articular bone becomes involved According to Erlacher, an improved roentgenographic technic indicates that a tuberculous focus in bone almost always begins as a small, isolated circumscribed focus in the capsule or in the region of a joint but not involving it Early eradication of this focus (by radical extirpation) should be attempted even though rupture into the joint threatens “The advantage of complete cure at one stroke is so great that one may with confidence assume the risks inevitably involved” Such a procedure is possible, according to Erlacher, in about 25 to 30 per cent of cases, and gives results obtainable by no other method It allows rapid, firm healing, decreases the duration of treatment a quarter to half, and in many cases preserves normal motion

TUBERCULOUS RHEUMATISM

Poncet in 1897 described “rhumatisme tuberculeux” as a condition somewhat resembling acute rheumatic fever with pyrexia, pain and swelling of several joints, leading shortly to frank tuberculous arthritis of a single joint Others broadened this concept of the disease and advanced the notion that, in some cases, it resembled atrophic arthritis, in others, hypertrophic arthritis, and in still others, juvenile Still’s disease Some believed it due to an actual tuberculous infection with bacilli in joints The majority, however, have suggested that an atypical tuberculous lesion was present—atypical in that actual tubercle bacilli were absent from joints, the reaction being one of articular allergy to a distant tuberculous focus Just as there has been no agreement as to the clinical picture of tuberculous rheumatism, so there has been no agreement as to its pathologic or roent-

genographic picture. Hence the condition has been accepted by few clinicians outside of France. In France, however, 12 of 16 "rheumatism specialists" interviewed by Slocumb⁹⁹ considered the entity established.

The argument has sharpened since Lowenstein and Reitter (1928) reported that, by a special technic, they could obtain tubercle bacilli in 70 per cent of cultures from blood and synovial fluid of patients who presumably had atrophic arthritis (also from the blood of patients with chorea). Very few have been able to confirm this work (Kallor, 1932) although two French clinicians reported to Slocumb their ability to obtain such positive cultures in 10 per cent of cases of chronic polyarthritis. Criticism of the work of Lowenstein and Reitter was summarized by Tan¹⁰⁰: a difficult procedure is rendered more difficult by the constant change of method, animal inoculations were not used to determine whether the tubercle bacilli recovered in cultures were virulent or not, bacteriologists who learned the method in Lowenstein's laboratory could not obtain the same results elsewhere.

Criteria considered necessary by some for a diagnosis of Poncet's rheumatism were as follows (Kubischky¹⁰¹): (1) the disease under study should be refractory to salicylates, (2) endocarditis should be absent, (3) non-articular tuberculosis should be present, also, (4) a positive tuberculin test, (5) there should be positive animal inoculation from synovial fluid (some would also add, from blood), and (6) there should be a predominance of mononuclear cells in synovial fluid. In this country and in England the entity has been accepted by very few investigators¹⁰² and rejected by the majority^{103, 104}.

Copeman¹⁰² believed that tuberculous foci, at times latent and unsuspected, may be the underlying cause of certain cases now called "rheumatoid arthritis." To support this view two cases were reported.

A 49 year old woman had multiple arthritis of the rheumatoid type following tonsillitis. Her parents had both died of tuberculosis, she had presumably never had it. Sixteen months later, aside from the joints, physical examination, including that of the lungs, was negative. (No roentgenograms of the lungs had been taken as yet—Ed.) Intradermal tests to old tuberculin and to Parke Davis' "protein purified derivative (P P D)" were strongly positive. No focal or general reaction resulted therefrom. The complement fixation test for tuberculosis was positive, but blood cultures sent to Lowenstein's laboratory were negative for tubercle bacilli. An injection of tuberculin was then given for treatment. A notable reaction followed: fever, malaise, increased arthritis. Rales were then heard at the right apex, a roentgenogram showed possible pulmonary tuberculosis. The reaction subsided in a few days. Three months later the patient had a slight cough without sputum.

In the second case a woman, aged 20 years, had chronic monoarthritis of varying intensity in her knee. Two years later the sacroiliacs and the other knee became involved. The next year she was treated (by someone else) for superficial skin ulcers of the legs, presumably tuberculids. Biopsy of the right knee revealed nothing definite for tuberculosis. The next year Copeman found a negative complement fixation test for tubercle bacilli, negative roentgenograms of thorax and knee. The sacroiliacs showed osteitis. Fluid from the knees was negative for tubercle bacilli. Tuberculin tests were positive to both O T and P P D. Five days later one of the old tuberculid scars became indurated, and four days thereafter an acute exacerbation occurred in

the knees and an ankle. A blood culture, sent to Lowenstein, was positive for tubercle bacilli. The general reaction lasted several days.

(These cases are thought-provoking but not convincing. Results of blood cultures would have been more impressive had they been done, not in Lowenstein's, but in Copeman's laboratory, thus confirming the former's technique. It has long been shown that an exacerbation of atrophic arthritis may follow injections of several unrelated substances, such as milk, typhoid and other bacteria as well as tuberculin. There is therefore nothing necessarily specific about the articular reactions to tuberculin which proves them tuberculous. Furthermore, latent tuberculous foci may also be activated by a variety of substances, not just tuberculin [Hench, 1932]. In tuberculosis such reactions to tuberculin are also not necessarily specific.—Ed.)

Regarding the tuberculous nature of Still's disease very dubiously, Moncrieff¹⁰⁴ cited the observation of Grenet (1935) that positive tuberculin reactions were no more numerous in arthritic children than would be expected in a group of healthy children. Were tuberculosis an important causal factor in chronic polyarthritis or atrophic arthritis, the association of the two diseases should be, at least, not uncommon. Yet among 800 of Dawson's¹⁰³ patients with atrophic arthritis only three had (active) tuberculosis. In 4,499 cases of tuberculosis at Saranac Lake, Brown¹⁰⁵ found only 11 cases of atrophic arthritis. Hench¹⁰⁶ restated the conclusion reached by him and Brav (1934) that the existence of tuberculous rheumatism cannot yet be accepted without many reservations.

Although recognizing the insecurity of the entity and the validity of most of the criticism directed against it, Tan¹⁰⁰ cautiously accepted the idea that rheumatism is an allergic disease, a manifestation of articular hypersensitivity to many different bacteria, including tubercle bacilli.

(The few cases presented by Tan as possible examples of "tuberculous rheumatism" seem to us to have been poorly chosen. One patient had for 10 years what we would regard as typical atrophic polyarthritis. Salicylates gave no relief, endocarditis was absent, and residual pleurisy, slight fever, and a positive Pirquet reaction were present. "Animal inoculation" and blood cultures for tubercle bacilli were negative. We cannot therefore see the indications for a diagnosis of tuberculous rheumatism in this case. In another case a patient had pleurisy with effusion and pain and slight swelling of a foot and elbow. Fifteen months later fistulous tuberculosis of the foot developed, tubercle bacilli being found in the discharge and in sputum. The elbow was unchanged. This seems to us like a case of classical tuberculous arthritis, probably of two joints, and not a case of "tuberculous rheumatism." A third patient apparently had had recurrent rheumatic fever and carditis as a child. Some years later milary tuberculosis developed. Tan considered a possible connection between the two diseases, a connection which seems to us very remote. Two typical cases of Pott's disease were also described and the case of a woman who had repeated pain and swelling of a shoulder and elbow. At tonsillectomy tuberculous tonsillitis was found. Such cases as these do not clarify the issue, the ever present likelihood of unrelated coincident or subsequent disease being ignored. They strengthen our opinion that to date the syndrome of tuberculous rheumatism rests on insecure grounds.—Ed.)

Slocumb⁹⁹ found the treatment of "tuberculous rheumatism" in France to be the same as for atrophic arthritis, except that a few physicians were

using small injections of tuberculin Foerster¹¹ used gold salts with reported satisfaction

PNEUMOCOCCAL ARTHRITIS

Pneumococcal arthritis is rare. It generally occurs with pneumococcal pulmonary infection (secondary pneumococcal arthritis). Primary pneumococcal arthritis (without a pulmonary infection) occasionally occurs (as it did in 26 of 185 cases of pneumococcal arthritis collected by Plisson and Biousse, 1920). Occasionally a non-suppurative, but generally a suppurative monoarthritis is present from which pneumococci can be recovered. Even when the infection is purulent articular function is generally restored and ankylosis is rare. A case of the primary type was reported by Bloomberg.¹⁰⁷

A 27 year old negress developed fever and a hot, swollen, tender left big toe. Aspiration of the first metatarsophalangeal joint one week later revealed 5 c.c. of thin flaky fluid and fibrin in which pneumococci, type IV, were found. Washed with mercury bichloride, the joint was symptomless four days later. Six weeks thereafter the left ankle and left wrist became involved. Aspiration of the wrist was not done, aspiration of the ankle revealed 15 c.c. of fluid, culture of which was negative. Repeated blood cultures were negative. Roentgenograms of joints were negative. Further treatment consisted of injections of a vaccine of pneumococci and streptococci. Articular restitution was complete.

(Pathological studies were not done. Such studies were recently reported in one case by Allison and Ghormley [1931]—Ed.)

SYPHILITIC ARTHRITIS AND CHARCOT'S DISEASE OF JOINTS

Syphilis may affect joints directly as a syphilitic synovitis or arthritis, or indirectly as an osteoarthropathy ("Charcot joint") secondary to syphilitic tabes dorsalis. Illustrative of the former, Myers³⁹ presented the case of a boy "probably with congenital syphilis, with recurrent acute arthritis of both knees."

This boy, an orphan aged 15 years, knew nothing about his family history. At the age of 13 both knees became tender, painful, and swollen for one month and recovered fully under rest alone. Two years later they again became swollen, painful, red and tender. Slight fever and adenopathy were present. Roentgenograms of joints were negative. The Wassermann reaction was positive on blood and on synovial fluid, cultures of joint fluid and the guinea-pig test were negative. Adenopathy disappeared and the joints fully recovered during treatment with neoarsphenamine.

(No diagnosis was definitely given but that of congenital syphilis and recurrent acute syphilitic arthritis is inferred to have been given. The diagnosis of congenital syphilis was apparently based on the idea that the boy was too young to have acquired syphilis. However, no stigmas of congenital syphilis were present and the boy may very well have acquired syphilis. The diagnosis of syphilitic arthritis was apparently made on the basis of the positive Wassermann reaction on synovial fluid and the remission in symptoms coincident with antisypilitic treatment. These data seem to us insufficient for the diagnosis. Myers admitted "the presence of positive Wassermann reactions on blood and synovial fluid cannot be considered proof of the etiology of the arthritis." Wassermann reactions on synovial fluid of normal joints tend to follow

those on the blood of syphilitics (Forkner, 1930) Had the reaction been negative on blood but positive on synovial fluid, it might have been more significant as far as joints were concerned (Kling, 1932) A diagnosis of syphilitic arthritis should in part rest on the success of antisyphilitic treatment after other treatment has failed In this case the cessation of arthritis during antisyphilitic treatment suggests, but does not prove the nature of the joint disease Arthritis may have been incidental, the previous attack having subsided entirely on rest alone It might be suggested that the patient had recurrent syphilitic synovitis [Clutton's joints], but not arthritis However, in this condition there is little if any redness, tenderness or pain—Ed)

Hypermobility and marked instability of joints are often features of "Charcot joints" Some kind of immobilization is generally required Cleveland¹⁰⁸ again presented evidence that immobilization by fusion of such joints is possible, though difficult At first, operation on a patient had produced a pseudo-arthritis in spite of prolonged postoperative immobilization, later, fusion was successfully accomplished

UNDULANT (MALTA) FEVER BANG'S DISEASE BRUCELLOSIS

The reported incidence of this disease in the United States is as follows in 1926, 46 cases, in 1927, 217, in 1928, 649, in 1929, 952, in 1930, 1420, in 1931, 1351, in 1932, 1326, in 1933, 1659, and in 1934, 1787^{109, 110} The increase is believed to be in part a true one and not just due to increased recognition of the disease Recent experiences with the disease in Tennessee, New Mexico, Iowa, New York (both city and state), Canada and Scotland were reported¹¹¹⁻¹¹⁶ The disease increasingly presents an industrial hazard to veterinarians, dairymen and meat packers, large numbers (26 to 92 per cent) of whom have it in latent form (Meyer and Geiger¹¹⁷)

Bones and joints are commonly affected (50 to 60 per cent of cases¹¹⁶), manifestations being arthralgia (migratory, often resembling rheumatic fever), myalgia, non-suppurative or suppurative arthritis, suppurative spondylitis, osteoperiostitis, or osteomyelitis The general symptoms of irregular prolonged fever, chills, anorexia, sweating, weakness, loss of weight and so on are not specific enough for diagnosis Recourse must be made to laboratory tests which, however, must be carefully interpreted as their results are variable in different stages of the disease and in different patients Criteria for diagnosis (Evans, 1934) include (1) cultivation of the organism from blood or excretions (or joints), cultures often being negative in acute, and more often negative in chronic, cases and most frequently positive in a pyrexial period, (2) positive agglutination test (usually above 1:1000, sometimes only 1:80 or 1:160), however, this may mean only that the patient has had the disease some time, it may be negative even in severe cases, tests in 5 to 16 per cent of cases being negative¹¹⁸, and (3) intradermal test with *Bacillus melitensis* antigen (vaccine), this test, however, may remain positive long after recovery, and normal people may develop cutaneous hypersensitivity thereto Specific and nonspecific cutaneous reactions can be easily differentiated, however, according to Fa-

vorite and Culp¹¹⁰ In undulant fever the blood picture resembles that of typhoid fever: leukopenia, lymphocytosis, and during fever a marked left shift of polymorphonuclear neutrophils¹¹⁰ Angle¹¹⁸ doubted the practicability of Huddleston's test of the opsonocytophagic power of the blood toward *Brucella* organisms

New cases with involvement of the locomotor system have been reported^{112, 113, 121-121} Present were migratory arthralgia or a migratory polyarthritides, a swollen left wrist with osteomyelitis from which *Brucella* organisms were isolated, and destruction of two or three contiguous vertebral bodies and intervertebral disks in various regions of the spine (Described as "spondylitis," osteomyelitis was apparently present—Ed)

Treatment When joints are less seriously involved they are treated symptomatically, when purulent lesions are suspected or obvious, aspiration and drainage are desirable both for diagnosis and treatment Frames and braces may be necessary for spinal lesions (Snyder¹²¹) For the primary condition many consider the various medicines used (including neoarsphenamine) as of no value^{110, 125} A patient of Ching's¹²⁶ apparently responded to neoarsphenamine Satisfactory response to a triple typhoid vaccine febrile reaction in one case was reported by Beaumont and Page¹²⁷ Transfusions may be helpful¹²³ Vaccines of *Brucella* organisms are of debatable value some are disappointed with them, others regard them highly^{110, 111, 118, 125, 128, 129} Convalescent immune serum was used in one case with apparent success by Kretzler¹³⁰ and Kennan¹³¹ after vaccine had failed Further experiences with their new antiserum were reported by Wherry, O'Neil and Foshay¹³² 20 patients "responded favorably", two were doubtfully improved, four unimproved Failures were believed due to inadequate potency of earlier serums and to insufficient doses Foshay's *Brucella* antiserum was recommended by Ashworth and Pickney¹¹⁰

Of interest also are historical notes^{109, 111, 118, 133}, studies on the bacteriology¹¹⁵ and on the immunology of the disease^{134, 135}, its experimental production,¹³⁶ and its spontaneous occurrence in dogs¹³⁷

PYO-ARTHROSES PURULENT (SEPTIC) ARTHRITIS

As noted, gonococci or pneumococci may produce purulent arthritis The commonest form of pyo-arthritis in adults is from gonorrhea Pyo-arthritis is commoner in children, when it is generally caused by *Staphylococcus aureus* or hemolytic streptococci, usually secondary to juxta-articular epiphysitis or osteomyelitis Additional etiologic factors in Veal's¹³⁸ cases were abscesses, boils, infected burns, staphylococcal pneumonia, streptococcal sore throat, acute tonsillitis, acute torticollis, and postoperative infection of a popliteal aneurysm, in Inge and Liebolt's cases¹³⁰ otitis media, pyelitis and purulent cervical adenitis, in Overton and Meyerding's cases¹⁴⁰⁻¹⁴³ a knife stab and a nail wound The source of infection is often undetermined Monarthritides is generally present, rarely polyarthritides A hip or knee is generally affected, less commonly an ankle, elbow, or shoulder

The usual symptoms are fever, chills, redness, swelling, much tenderness, muscle spasm and articular distention from fluid. It is agreed^{138, 139, 144} that although roentgenograms show alterations in joints after a number of days, they are not helpful in early diagnosis so important for treatment if articular function is to be saved. For early diagnosis aspiration of the joints is most valuable and, if the first tap is "negative," should be repeated in suspected cases. One should try to be certain, however, that arthritis and not just periarthritis is present^{141, 143}. Insertion of a needle through a purulent periarthritis (as from a stab wound) may infect an otherwise unaffected joint. Cultures of aspirated pus may be negative, possibly owing to the bactericidal properties of synovial fluid¹⁴⁵. Cultures were negative in 55 per cent of Veal's¹³⁸ 68 cases, and in 39 per cent of the 36 cases of Inge and Liebolt¹³⁹. Cultures revealed staphylococci (generally aureus) in 25 per cent of Veal's cases, in 36 per cent of Inge and Liebolt's cases, in 60 per cent of Slowick's¹⁴⁴ 60 cases, and in 100 per cent of Martland's 8 cases¹⁴⁶. Streptococci (generally hemolytic) were recovered in 15 per cent of Veal's cases, 32 per cent of Inge and Liebolt's cases and in 39 per cent of Slowick's cases. Other bacteria occasionally recovered were *Bacillus pyocyaneus*, pneumococci, and mixed staphylococci and streptococci.

Three rarer forms of purulent arthritis were reported. A case due to *Micrococcus tetragenus* was reported by Reiman,¹⁴⁷ who found eight such cases with arthritis and two with arthralgia in the literature. Hematogenous osteomyelitis and pyo-arthritis due to *Salmonella supestifer* (hog cholera bacillus) were present in the case reported by Weaver and Sherwood¹⁴⁸, six other cases of such a pyo-arthritis have been reported. Thirty cases of pyo-arthritis due to *Haemophilus influenzae* (*Bacillus influenzae* of Pfeiffer) have been recorded and Peterson reported another¹⁴⁹.

Treatment Treatment concerns the patient, the primary focus of infection and the joint. Surgeons of the seventeenth and eighteenth centuries were content to try to save the life of a patient with pyo-arthritis. In the nineteenth century they tried to save life and limb, ankylosis being a small matter. In the twentieth century the aim is to save life, limb and articular function¹³⁹. All agree that early repeated aspirations or drainage are imperative, but opinions differ on the methods of drainage (simple aspiration, aspiration and irrigation, incision and drainage, arthrotomy). The procedure must be suited to the case under treatment. Amputation is even occasionally necessary^{138, 150}. Indications for these different procedures have been restated by several^{19, 138, 139, 146, 150-153}. Splints and casts may be necessary^{144, 146}. Postoperative physiotherapy and early joint motion are favored by some,^{139, 145} used cautiously by others¹³⁸. Of three plans in current favor (1) drainage and active mobilization (Williams, 1919), (2) drainage, immobilization and traction (Harris, 1925) or (3) joint washing, closure of the joint and temporary immobilization (Cotton, 1916, 1920), Jones¹⁴⁵ favored the third, that is arthrotomy, washing the joint with physiologic saline solution or with 1:15,000 bi-

chloride solution in saline, and then suturing. Matland¹¹⁶ favored the use of proflavine intra-articularly, and euflavine and antistaphylococcal serum intravenously. Staphylococcal bacteriophage for purulent staphylococcal arthritis has been advocated (Rice, 1930, Wiant and Mirallie, 1931, Flury, 1931). Its value was questioned by Gregorie (1931). Inge and Foumey¹¹⁷ found it of no value to one patient, and also not helpful in the treatment of experimental staphylococcal arthritis in dogs. Bacteriophage is probably inactivated by body fluids.

Staphylococci are not killed even by the application of 100 hours of heat at 106.7° F (41.5° C). Staphylococcal infections would thus seem to be impervious to fever therapy. However, a diabetic patient with an apparently hopeless case of staphylococcal septicemia was reported as having recovered after fever therapy prescribed in desperation (Hartman¹¹⁸).

Course and Prognosis, Results of Treatment. The course of pyoarthrosis is limited and not progressive as in "nonspecific infectious" (atrophic) arthritis. Little loss of function may result if treatment is adequate, at other times great destruction and deformity ensue. Arthroplasty and other corrective procedures are later indicated^{20, 152, 153}.

Of Slowick's¹⁴⁴ patients, 22 per cent regained excellent joint function, 40 per cent good or fair function. The mortality was 20 per cent in his cases, 18 per cent in Veal's¹³⁸. As the cases of Inge and Liebolt again showed, results are often (54 per cent) good when the condition is not complicated by bone infection, poor otherwise¹³⁹.

TYPHOIDAL ARTHRITIS AND SPONDYLITIS

Typhoidal arthritis occurs in 1 to 10 per cent of cases of typhoid fever. Since typhoid fever is becoming rare in the United States, typhoidal arthritis is also becoming very rare, particularly "typhoid spine," one of the less common varieties of typhoid arthritis. No recent reports have been available for our Reviews. Up to 1932, only about 150 cases of typhoid spondylitis were reported (Wang and Miltner, 1932) and only one necropsy recorded (Rugh, 1915). Gambee¹⁵⁵ briefly reviewed the symptoms of the condition and gave 17 references thereon from 1889 (Gibney, who named "typhoid spine") to 1932. In light of newer knowledge of the physiology of the intervertebral disks, Gambee has attempted to explain the pathogenesis of the different varieties of "typhoid spine" and why lumbar vertebrae are particularly affected. Appended was a case report on operative drainage of a vertebral abscess which developed four years after the patient had apparently recovered from typhoid spine.

A boy (age unstated) had typhoid fever in 1929, complicated by empyema and a pararectal abscess. Severe lower thoracic and lumbar backache developed, with fever and muscle spasm, and lasted about three months. A diagnosis of typhoid spine was made (no mention is made of roentgenograms—Ed). Four years later, after swimming, low backache, muscle spasm and kyphosis developed. Roentgenograms revealed fusion of the third and fourth lumbar vertebrae and partial obliteration of the inter-

vertebral disk, interpreted as a long-standing affair more like typhoid spondylitis than tuberculosis. The Widal test was negative, no typhoid bacilli were found in stools. Leukocytosis (15,750 cells) was present. At operation, an abscess of the affected vertebral bodies and intervertebral disk was drained. On culture the pus revealed a few gram-positive cocci but no typhoid bacilli. The guinea-pig test for tuberculosis was negative. Pain and fever promptly subsided and convalescence was uneventful.

(It is regretted that no report on roentgenograms during the initial fever was given and that the recent roentgenograms were not reproduced. Considering the prolonged viability of typhoid bacilli in the human body (e.g., in the gall-bladder) a diagnosis of "typhoid spine" seems possible, but in the absence of bacteriologic proof the diagnosis is presumptive.—Ed.)

ARTHRITIS WITH CHRONIC ULCERATIVE COLITIS

Of 1,500 patients with chronic ulcerative colitis of the type believed due to the diplostreptococcus of Bergen, 60 had coincidental arthritis. Arthritis was the commonest "complication" except polyposis (in 130 cases) and stricture of large intestines (in 110 cases). Bergen¹⁰⁰ and Hensch¹⁰¹ thought that this association cannot be explained satisfactorily on the basis of coincident association of two independent diseases, but that a specific complication and a specific type of arthritis may be present in some of these cases. Analysis revealed four types of relationship: (1) that in which arthritis preceded the colitis by a fairly long time, the arthritis was considered unrelated to the colitis and was generally of the atrophic, rarely of the hypertrophic, type (as chronic ulcerative colitis is a disease of early life), (2) that in which both atrophic arthritis and ulcerative colitis came on more or less together but in which each disease thereafter seemed to progress quite independently, neither being particularly affected by variations in the other, (3) that in which an arthritis resembling atrophic arthritis affected a patient who already had severe ulcerative colitis, but in which exacerbations in joints appeared during remissions, not with exacerbations, of colitis, and (4) the more common type of association—that in which a subacute arthritis appeared with the onset, or more frequently with a subsequent exacerbation, of severe colitis after which the patterns of both diseases showed a striking conformity, remissions and exacerbations of both appearing simultaneously, the joints often being relieved by measures directed to the bowels.

The first two and possibly also the third type of case were believed to represent an unrelated coincident association of ulcerative colitis and atrophic arthritis. The fourth and more common type of case was tentatively thought to represent a specific relationship. One, or several, large or small joints were moderately or severely affected. Periarticular involvement was often more noticeable than intra-articular. Suppuration was not encountered. The appearance and roentgenograms of joints resembled those of atrophic arthritis. In all of these cases the characteristic diplostreptococcus of Bergen was isolated from intestines, and about 80 per cent of the animals injected intravenously therewith were found to have intestinal lesions strikingly like those of patients. However, arthritis was not produced in a single

animal (a significant fact in the face of the presumed case with which arthritis is produced in animals by streptococcal injections—Ed) This suggested that the articular lesion in man may result, not from metastatic invasion of the specific diplostreptococcus, but from related "toxins" or an unidentified secondary invader

Points which seemed to distinguish the arthritic entity were (1) the clinical relationship between the appearance, activity, and recovery from the colitis and the arthritis, (2) the greater tendency to periodicity and to more complete remissions (at least after earlier bouts) in the arthritis than is usually seen in atrophic arthritis, (3) the striking improvement that may occur in the joints from use of specific serum (antistreptococcic serum therapy for ordinary atrophic arthritis has generally been abandoned as useless), and (4) the fact that although certain streptococci can be isolated from various sites, including the intestines and stools of patients with atrophic arthritis there were certain cultural and physical differences between them and the diplostreptococci isolated in such cases

(The foregoing data are admittedly incomplete and inadequate for the establishment of a new entity Only a few cultures of synovial fluid or tissue have been made as hydrophilia was not a feature Cultures revealed no specific diplostreptococci Pathologic data are not yet presented Until more information is forthcoming the reader will probably prefer to assume that a coincident and more or less unrelated atrophic arthritis was present with colitis Those who glibly incriminate more or less symptomless intestines as the cause of atrophic arthritis should note the relative rarity of articular disease in the presence of severe ulcerating lesions of the intestines with blood, pus and multiple stools Arthritis complicates ulcerative colitis in only 4 per cent of cases, typhoid fever in 10 per cent or less, bacillary dysentery in about 3 per cent, and amebic colitis rarely if ever Those who "blame the bowels" may find some comfort in the evidence which shows that arthritis and intestinal diseases can be causally related [by hematogenous, not the enterogenous route], but the rarity of a proved relationship should give one pause

However, there is need for complete open-mindedness on this difficult problem As many now tend to incriminate symptomless infections of nasopharynx as foci for atrophic arthritis, so some argue that symptomless gastrointestinal infection or "faulty elimination" may play a significant role either as a primary or predisposing cause of arthritis—Ed)

RHEUMATIC FEVER

Predisposing Factors A few new data are available on predisposing factors geography and climate, seasonal influences, social and hygienic conditions, heredity, and the factors of age and sex

Relation of Geography and Climate to Incidence Further evidence is presented indicating that rheumatic fever is much less common in the southern than in the northern United States^{29, 157} The incidence diminishes progressively from latitude 50° to 29° (as it does also for scarlet fever but not for acute glomerulonephritis, a fact which is strange¹⁵⁷ if hemolytic streptococci are the cause of each of these diseases) The incidence of mitral stenosis in New Orleans (latitude north 29°) is one-twentieth that in Boston

(latitude north 42°)²⁰ Either there is much less rheumatic fever in the South or it does not affect the heart as it does in the North. The incidence of rheumatic carditis in two Dallas, Texas, hospitals (latitude north 32°) was low¹⁵⁸. Of 32,753 medical admissions to a hospital for private patients, 0.34 per cent (114) had rheumatic fever, of which 43 per cent had arthritis, 37 per cent tonsillitis. Only two patients had chorea. Of 10,800 medical admissions to a hospital for charity patients, 1.01 per cent (110) had rheumatic fever, of which 53 per cent had arthritis, 36 per cent tonsillitis. There were two cases of chorea. These figures indicate that rheumatic polyarthritis is less common, chorea much less common, in Texas than in the North.

Rheumatic fever is common in England and Scotland. On a given day in February 1935, there were 99 cases of rheumatic carditis in Edinburgh hospitals. In four large hospitals, one in 8 of all medical patients was suffering from rheumatic carditis (Ritchie¹⁵⁹). At Queen's Hospital, Birmingham, 4.3 per cent of the 5308 medical admissions between 1924 and 1928 were for rheumatic carditis; these cases formed a third of all admissions for cardiovascular diseases (Brenner¹⁶⁰).

According to Rogers (1924) and Clarke (1930), rheumatic fever and carditis are practically unknown in the tropics. New statistics refute these contentions. Cairns, Australia, a city of 13,000 people in latitude 17° south, a city well within the tropics, had 666 cases of acute rheumatism in 11 years (Cooper¹⁶¹). Mortality statistics from several Australian cities indicate that the severity of rheumatic fever varies with the latitude, becoming progressively greater as one goes from tropical (northern) Australia to the temperate (southern) portion. Usual manifestations of rheumatic fever were present in the cases of Wig¹⁶² in the Punjab (Lahore). According to Kutumbiah¹⁶³ 143 cases of rheumatic carditis were seen in three years at the King George Hospital, Vizagapatam, South India, latitude 16° to 20° north—wholly within the tropics. (The clinical data seem quite acceptable. No pathologic data were presented—Ed.) The report to McKinley³ from Sprawson, Director General of the Indian Medical Service, indicated that rheumatic fever was to be found generally throughout India. ("The approximate number of cases of rheumatic fever" is given at 276,611—which seems to include cases of "febrile endocarditis" and of "rheumatism". No further explanation is given, the figures cannot be interpreted—Ed.)

Seasonal Incidence As elsewhere so in Minneapolis, rheumatic fever in children most commonly appears during early spring (February to April) and late fall (October to December)¹⁶⁴.

Social and Hygienic Conditions Some think that the poorer the child the more likely he is to get rheumatism. Patients studied by Taran¹⁶⁵ all belonged to the poorest class of the community in Brooklyn, New York. Others think it is not the poorest, but the "decent poor," children of the respectable working classes, that are chiefly attacked¹⁶⁶. The cases of Preston¹⁶⁶ seemed to support this view. In English schools for poor children, rheumatic fever is common, in those for children of the upper classes it is

almost unknown. Eton, a school of 1,100 boys has had only one case in 17 years,¹⁶⁷ but in the town of Eton the elementary school children are frequently affected.¹⁶⁸

Factor of Heredity and Family Incidence Rheumatic fever is a familial disease. Whereas Shapiro¹⁶¹ found it in only 15 per cent of families of non-rheumatic children, he found it in 47 per cent of families of his rheumatic children, often several members of a family having been affected. Among 458 children with rheumatic carditis seen by Gilkey,¹⁶⁹ in the families of 105 children there were two cases, in the families of 20 children three cases, and in the families of 10 children four cases of rheumatic disease. Preston¹⁶⁶ found a familial incidence in 45 per cent of his cases of acute rheumatism with carditis. In his 200 cases Wilkinson¹⁶⁷ found a familial incidence of nearly 70 per cent. However, in a study of 24 patients less than three years of age with rheumatic fever McIntosh and Wood¹⁷⁰ found no simultaneous rheumatic fever in the home and felt that the frequency with which post-rheumatic infection had occurred in the parents of these children was no greater than one would expect to find in any family. (No control figures were given by McIntosh and Wood, however—Ed.)

Factor of Age Rheumatic fever and carditis generally first appear between the ages of six and 12 years as current statistics again show. Of Taran's¹⁶⁵ 169 patients, 88 per cent were from six to 12 years of age. The peak incidence of onset was between five and six years in Shapiro's cases,¹⁶¹ and between 11 and 15 in Ritchie's 244 cases.¹⁵⁹ Rheumatic fever may first appear at any time from birth to old age. Forty cases in infants less than a year old have been reported (Paul, 1932). Although rare under the age of three years, it probably occurs more frequently than is recognized. McIntosh and Wood¹⁷⁰ found references to 40 patients in the first three years of life. In the past 25 years at Babies Hospital, New York City, 24 cases of rheumatic fever affecting children less than three years old were seen. Necropsy was performed in six cases. The impression that rheumatic fever in infants is somewhat different than in older children was not definitely confirmed. Of children less than three years old, 96 per cent exhibited carditis, 46 per cent polyarthritis. However, the clinical picture was "more often that of a general infection than of a specific disease entity." "Several" of Shapiro's patients¹⁶¹ were less than two years of age.

The disease first appeared, once after the age of 50 years and once after the age of 60 in the cases of Davis and Weiss,¹⁷¹ occasionally after the age of 60 in those of De Graff, Lingg and Cohn.¹⁷² According to Ferris and Myers¹⁷³ when the disease begins in patients more than 60, it is similar to that in younger persons except that polyarthritis is possibly less intense and more persistent. Of six such patients, three died and the characteristic pathologic changes were found at necropsy. Carditis developed in the remaining cases. With appropriate data one should therefore not hesitate to

make a diagnosis of an initial attack of rheumatic fever simply because a patient is more than 50 or 60 years old

Factor of Sex Among children, rheumatic fever presumably affects girls more often than boys in a ratio of 6:4. Gilkey's patients¹⁶⁹ with rheumatic carditis included 275 girls, 183 boys. There were 142 females (62 per cent), 85 males (38 per cent) in the series of Brenner,¹⁶⁰ who stated that up to the age of 20 the incidence in males about equalled that in females. The preponderance of affected females begins only after the age of 20 years. Rheumatic carditis is thus less common but more severe in males and gives rise to symptoms earlier. However, in Taran's¹⁶⁵ group of 169 children were 85 girls, 84 boys. Of those with carditis, half were girls, half boys.

General Symptomatology The familiar and varied symptoms were again described^{159, 167, 170, 171, 175}. Many "growing pains" of children are not rheumatic. Differentiations of the rheumatic and non-rheumatic variety were recorded. Rheumatic growing pains, according to Shapiro¹⁶⁴ are commonly articular, affect joints of arms as well as legs, are generally better at night if the patient is warm, worse in daytime and on walking, particularly during the first hour of the day, are often associated with a little fever, articular swelling and heat, and with other signs of rheumatic activity: frequent nose-bleeds, pallor, undernourishment, fever, abdominal cramps and carditis. The non-rheumatic variety are not so generally articular, are usually diffusely and vaguely located in muscles of legs and thighs, appear or are worse at night soon after going to bed, may be gone in the morning, are not present on motion, produce no limping or significant stiffness during the day and are not associated with fever or other evidences of ill health. (Shapiro's differentiation suggests one between arthralgia and myalgia, not necessarily one between rheumatic and non-rheumatic types of pain —Ed.)

Rather than being better at night, rheumatic pains, according to Rosenblum,¹⁷⁶ may be particularly noticeable at night although they may occur at any time. Non-rheumatic pains in the limbs of the tired, weak child occur only in the legs, often only during or immediately after exercise, and disappear with rest. In case of doubt treatment with salicylates is suggested. "The pains of true rheumatism subside with adequate doses of salicylates."

(There is no reason why many non-rheumatic pains should not also be somewhat relieved by salicylates. The differentiation seems inadequate since the analgesic action of salicylates on rheumatic pain is only relatively, not absolutely, specific —Ed.)

Rheumatic growing pains may be muscular as well as articular, Preston stated¹⁶⁶. If muscles of calves, thighs or arms are definitely hard and painful to the touch, they should be considered rheumatic. Many non-rheumatic pains are produced in children by orthopedic defects, which Preston¹⁶⁶ and Elman¹⁷⁷ frequently found in supposedly "rheumatic children." These defects included flat feet, hammer toe, kyphoscoliosis, hallux valgus, hallux rigidus, genu valgum, and pes cavus.

The frequency of tonsillitis and upper respiratory infections as precursors of rheumatic fever has been noted by many. Among 458 rheumatic children Gilkey¹⁶⁹ noted that 70 per cent had had a preceding tonsillitis or recurrent sore throat, and 10 per cent recurrent colds. Respiratory infections occurred as a precursor in 42 per cent of the rheumatic infants in McIntosh and Wood's cases¹⁷⁰. The reports of Coburn and Pauli are well known, they have further reported¹⁷⁸ that of 17 patients whose throats became infected with an epidemic strain of a toxin-producing hemolytic streptococcus, 14 had a rheumatic exacerbation. Rheumatic fever was often, but by no means always, precipitated by respiratory infections in the cases studied by Bland and Jones¹⁷⁹ respiratory infections were noted in 75 per cent of those with recurrences. Less than 10 per cent of rheumatic attacks experienced by the patients of Wheeler, Ingerman, DuBois and Spock¹⁸⁰ were preceded within three weeks by respiratory infections.

(Variable opinions on the etiologic significance of prodromal respiratory infections will be discussed later under "etiology and pathogenesis"—Ed.)

Kutumbiah¹⁶³ noted that polyarthritis is not nearly as frequent a manifestation of rheumatic fever in children as in adults, at least in the tropics. Of his patients with juvenile rheumatic carditis only 18 per cent had polyarthritis.

Special Symptomatology and Pathology Cardiovascular. Last year (1935) was the centennial of Bouillaud's recognition of the connection between rheumatism and endocarditis. The course of rheumatic carditis has been again reviewed^{159, 165, 167, 171, 172}. In the large cities of the United States about 1.5 to 2 per cent of school children have some cardiac disability. Thus in Chicago about 10,000 children would be so affected¹⁷⁶. The annual mortality from rheumatic carditis in England is 12,000 to 30,000. Wilkinson¹⁷⁷ estimated that, in England, there are more than 50,000 children and not less than 100,000 adults with rheumatic carditis. Most rheumatic patients develop carditis, particularly infants. Of the latter seen by McIntosh and Wood,¹⁷⁰ 96 per cent had carditis. Newer statistics on the types of cardiac lesions present confirm previous reports^{160, 163, 165, 166, 170, 177}. For example, in Brenner's¹⁶⁰ 127 necropsies (with chronic valvulitis) the mitral valve was involved in 99 per cent, aortic in 66 per cent, tricuspid in 19 per cent and the pulmonary in none. According to Brenner, there are three types of cardiac involvement: (1) the acute type, running a fulminating, fatal course without time for chronic valvulitis to develop, (2) the subacute type, with repeated attacks and the development of valvulitis, (3) the chronic type, in which severe carditis never occurs but there are many minor attacks, often entirely overlooked, and in which mitral rather than aortic disease eventuates.

Rheumatic tricuspid stenosis is rare. Only 250 cases were reported up to 1933. A case observed by Clemens¹⁸¹ was unusual because the tricuspid ostium was extremely narrowed, symptoms were those of mitral stenosis, other valves were normal except for mitral insufficiency and slight mitral

valve sclerosis, and the right auricle was only slightly enlarged in spite of the extreme tricuspid stenosis

Aschoff bodies are rarely found in the myocardium during the first four weeks of the disease, thereafter, they are present in about 90 per cent of cases. An earlier lesion which some believe to be specific for rheumatic fever, may be found—the “fibrinoid degeneration” of Klinge. Chiari¹⁸² reviewed its structure: loosening of interstitial tissue, areas more strongly colored by eosin, and enlargement and irregular swelling of connective tissue fibers—at first with no alteration in nuclei and little or no surrounding cellular reaction. Chiari supported the view that the discovery of such lesions indicates the rheumatic nature of a condition even when Aschoff bodies are absent.

Points in the differentiation of functional and organic murmurs and congenital and acquired carditis were restated by Lyon^{171, 175} and by Dwan.¹⁸³ An apical systolic murmur, so often found in children, is of no significance unless there has been a recent attack of rheumatism or chorea or unless there is present cardiac dilatation, tachycardia or a lack of response to effort. Malmer's epinephrine test (1932), sound tracings, and microphonic amplification are recommended by Dwan to clarify murmurs.

With rheumatic carditis, pericarditis is not uncommon (about 17 per cent of Brenner's¹⁶⁰ cases). Eight of nine cases of rheumatic pericarditis seen by Antell¹⁸⁴ began during polyarthritis. Cardinal signs are friction rub, an enlarging heart outline, and certain alterations in the left thorax posteriorly: flatness and diminution of breath sounds at the left base, dullness, bronchial breathing, bronchophony and pectoriloquy at the angle of the left scapula. Electrocardiograms were of no aid to Antell in diagnosis. Rheumatic pericarditis alone is uncommon. Yater and Hedley¹⁸⁵ reported the case of a young woman with recurrent rheumatic fever who had pericarditis and septicemia with “alpha prime streptococci”. At necropsy, myocarditis and endocarditis were not found. The organisms, injected into monkeys and rabbits, produced arthritis and ulcero-vegetative endocarditis.

Blood vessels are widely affected in rheumatic fever, and Gross and his colleagues^{186, 187, 188} have continued their studies thereon. Varied lesions of the coronary and pulmonary arteries, aorta, and the left auricle were depicted in photomicrographs.

Lungs A clinical diagnosis of rheumatic pleurisy is not often made. The studies of Starr and Parrish¹⁸⁹ indicate that pleurisy is commoner than supposed, as can be demonstrated if routine roentgenograms of the chest are taken during the active phases of rheumatic fever. Interlobar pleural thickening was found in 44 per cent of children with other manifestations of rheumatic fever, it was found in 14 per cent of those with chorea alone but in only 9 per cent of “normal” children.

Nodules The subcutaneous rheumatic nodule is “perhaps the most characteristic single sign of acute rheumatism”¹⁶⁷. Nodules may appear about joints, especially elbows, knees, carpometacarpal joints, wrists, ankles,

and about the occiput or iliac crests. They vary in size "from a pin's head to an almond," generally that of a "split-pea." They may appear in great numbers or be scanty, especially in infants¹⁵⁹ (They were present in 14 per cent of Coburn's cases, 1931—Ed.) In India they are the rarest of all rheumatic manifestations¹⁶³. In Elman's¹⁷⁷ ambulatory cases of rheumatic carditis none were found. Several, unusually large painless nodules were found by Davison¹⁹⁰ in the occipital, iliac and sacral regions of an eight year old boy. After three weeks they receded.

Skin Erythema annulare rheumaticum, described by Lehdorff and Leimer (1922) is "a specific exanthem associated only with rheumatic endocarditis." It appears following endocarditis, never at the onset of acute fever. Transitory in nature, it is often overlooked. According to Lehdorff and Leimer it occurs in about two-thirds of cases of juvenile rheumatic endocarditis. Abt¹⁹¹ observed it in six children (more frequently than subcutaneous nodules). The lesions are pale red or bluish-red semicircles or rings one to three cm. in diameter. They are always macular, never papular, and disappear without scaling or pigmentation. They are found on chest, abdomen, back and thorax, rarely on extremities and never on the face or mucosae. There is no itching, edema or hemorrhage.

Exudates McEwen¹⁹² hoped to find in pleural, pericardial or synovial exudates in rheumatic fever the same characteristic cells which he found (1932) in rheumatic granuloma, however, they were absent. Sixty-two arthritic, eight pleural and five pericardial exudates from 33 patients with rheumatic fever were compared with 35 similar exudates from patients with other diseases. In rheumatic fever there were 800 to 47,000 leukocytes per cu. mm. of synovial fluid, depending on the severity of the arthritis. The cells were nonspecific in character, being similar to those of other exudates.

Routine Laboratory Data (Electrocardiograms, Sedimentation Rates, Blood Counts, Roentgenograms) Each of 63 cases of rheumatic fever seen by Master and Jaffe¹⁹³ demonstrated electrocardiographic abnormalities, "unequivocal signs of severe myocardial involvement." Common ones were RST changes (85 per cent), elongation of P-R interval over 0.2 seconds (53 per cent), T-wave inversion (40 per cent), isoelectric T-waves (29 per cent).

(Master and Jaffe did not emphasize sufficiently here or in their previous report (1932) that electrocardiographic alterations may not be seen if only one or two tracings are taken, and that to demonstrate abnormalities in 100 per cent of cases it was apparently necessary to take daily tracings—"as far as possible daily electrical tracings were taken." It is not stated how many single tracings were negative, how soon in relation to polyarthritis the tracings became abnormal, how often only minor abnormalities were present—ones which are sometimes seen in "normal" persons—or the average number of "negative tracings" necessary to be obtained before a case is considered electrocardiographically "negative." Our experience is that single electrocardiograms are frequently negative during the first, or an early, attack of polyarthritis and that in many cases repeated tracings are necessary to obtain some abnormality—Ed.)

Lead IV, according to Levy and Bruenn,¹⁹¹ sometimes furnishes evidence of active rheumatic carditis when changes are not observed in the standard three leads, or it may render significant the minor changes in these three leads which otherwise might be regarded as of doubtful importance. Most frequently observed changes in Lead IV were alterations in the direction or voltage of the T-wave.

According to Brenner¹⁹⁰ electrocardiograms are of little use in the diagnosis of chronic rheumatic carditis. Alterations may indicate that some sort of lesion is present, and where it is, but not whether it is rheumatic or not.

Brakeley¹⁹⁵ found that among 100 children with milder degrees of rheumatic carditis electrocardiograms differed little from those found in normal children or those with functional murmurs. They added no information not obtained by physical examination, although they did furnish confirmatory evidence. Important changes to look for in rheumatic carditis are an increased height and breadth of the P-wave, accompanied by notching, increase in the P-R interval, slurring or notching of the QRS complex, inversion of T-wave in two or more leads, and right axis deviation.

The average sedimentation rate at one hour was found by Orme¹⁹⁶ to be 70 mm.

(Westergren's modification of Fahraeus' test was used. Some consider this method too gross to be of value and favor the method of Rourke and Ernstene, 1930.—Ed.)

Leukocyte counts should be done in all cases. Leukemia in children may occasionally present symptoms resembling acute rheumatic fever.¹⁹⁷

Relation of Rheumatic Fever to Other Diseases—To chorea. The relationship between rheumatic fever and chorea will be discussed later under "chorea."

To atrophic arthritis. Some believe that rheumatic fever and atrophic arthritis are different diseases, others that they may be different manifestations of the same disease. Dawson¹⁹³ and Boots³⁴ favor the latter view. Similarities are that both show familial tendencies, seasonal incidences are essentially alike, respiratory infections may precipitate either, and subcutaneous nodules of essentially similar type are found in each. There are marked dissimilarities: the age incidences are very different, carditis is rare in atrophic arthritis, common in rheumatic fever. The latter is also characterized by erythemas and by response to salicylates absent in the former. In atrophic arthritis, agglutinins to hemolytic streptococci are present but antistreptolysins are absent, in rheumatic fever the opposite condition obtains.

As evidence of a close relationship Young and MacMahon¹⁹⁸ reported cases in which chronic atrophic arthritis followed what was presumably rheumatic fever and in which mitral disease was present. From a study of pathologic findings in other cases (not these cases) they concluded that articular tissues in either disease presented no definite differentiation.

(The report is open to criticism. Thirty cases were collected, but data on only 10 were tabulated and then so briefly that the reader cannot form his own conclusions. Only two case reports were given and these are inadequate for one to accept the diagnoses given. No roentgenograms, electrocardiographic reports, serologic differentiation or pathologic studies in these particular cases were given. The report seems premature in that no cardiac pathology was available to prove that the carditis was of the true rheumatic variety (with Aschoff bodies, etc.) or of a "nonspecific type." Patients with atrophic arthritis do occasionally develop a nonspecific carditis (Boas and Rifkin, 1924). Patients with atrophic arthritis frequently state that their disease started as an "acute rheumatic fever" or "inflammatory rheumatism." Practitioners are generous with these terms in any acute arthritis, forgetting that acute atrophic arthritis may occur. Careful questioning commonly reveals that acute atrophic arthritis, not acute rheumatic fever, initiated the chronic arthritis. Even were a patient to present pathologic evidence of rheumatic carditis and of atrophic arthritis, it could not be concluded that the two were part of the same disease. One could only conclude that the patient had both diseases, a state of affairs occasionally quite permissible by the law of coincidence or the chances for a double simultaneous infection.—Ed.)

SHAPIRO¹⁰⁴ believed that juvenile rheumatic fever has little if anything in common with chronic arthritis. "In the hundreds of cases of rheumatic infection which I have followed for the past 12 years I have never seen one instance where the patient developed chronic arthritis directly following juvenile rheumatism."

To subacute bacterial endocarditis. About 4 per cent of patients with rheumatic fever later succumb to bacterial endocarditis (White and Jones, 1928). The majority (50 to 65 per cent) of patients with subacute bacterial endocarditis have previously had rheumatic fever. Ideas as to the nature of this close relationship are that (1) rheumatic and bacterial endocarditis are reactions of different intensities to the same infection, or (2) subacute bacterial endocarditis is a secondary infection superimposed (a) on old or healed rheumatic valvular lesions, or (b) on recent or active rheumatic vegetations. From a study of 26 cases Von Glahn and Pappenheimer¹⁰⁹ concluded that bacterial endocarditis in rheumatic patients is due to the superficial implantations of non-hemolytic streptococci on active unhealed (not old) rheumatic vegetations. It is not the old scarred valve that is predisposed to subsequent infection with bacteria, but the valve or auricular wall affected by fresh, unhealed verrucae or plaques. Active rheumatic vegetations are a necessary prerequisite to bacterial implantation.

Differential Diagnosis. Rheumatic fever must frequently be differentiated from acute atrophic arthritis, acute polyarticular gout, or acute gonorrheal polyarthritis or polyarthralgia. Master and Jaffe¹⁰¹ compared electrocardiograms in 63 cases of rheumatic fever and 50 cases of acute atrophic arthritis. In those with rheumatic fever significant electrocardiographic abnormalities were found in 100 per cent (when daily tracings were taken). In those with acute atrophic arthritis there was a complete lack of electrocardiographic evidence of myocardial disease. Thus the presence of a definite abnormality in a given case would speak for rheumatic fever.

(Master and Jaffe have accepted the criticism that the presence or absence of an abnormal electrocardiogram may have influenced them in making a diagnosis of one or the other disease, and admitted a recent tendency to do this but believed that the differentiation was accurate none the less. Before one can establish the practical value of this differentiation further data should be forthcoming, particularly on how early in the disease and after about how many tracings the electrocardiographic abnormality becomes apparent. The paying patient of moderate means cannot afford many serial electrocardiograms, and, as mentioned before, single tracings are frequently negative in the early stage of acute rheumatic fever when differentiation is most desirable—Ed.)

The early polyarthritic or polyarthralgic phase of gonorrheal rheumatism is often mistaken for rheumatic fever. Furthermore, a patient with chronic gonorrheal urethritis may develop rheumatic fever, the latter being regarded as gonorrheal polyarthritis. In such cases Myers³⁰ and Boots³⁴ base differentiation on the electrocardiogram, a positive or negative salicylate effect, bacteriology and cytology of synovial fluid, and the gonorrheal complement-fixation test.

An initial attack of rheumatic fever may occur after the age of 50 or 60 years. However, the commonest form of acute arthritis in males more than 40 or 50 years of age is from gout, according to Hench^{40,106}. It is commonly misdiagnosed rheumatic fever. The stage of acute rheumatic polyarthritis is usually considerably longer (20 to 50 days) than that of gout (7 to 20 days). The diagnosis of rheumatic fever should not be dismissed simply because a patient is more than 50¹⁷³. Differentiation is made on electrocardiographic evidence, estimation of the blood uric acid, effects of salicylates or colchicine, and on the clinical course.

Course and Prognosis. The course and prognosis of rheumatic fever are almost entirely that of its cardiac component. The course is generally one of remissions and exacerbations, with occasional arrest, but usually with a more or less relentless progression. Exacerbations are so frequently precipitated by respiratory infections that some regard the latter not as non-specific precipitating factors but as an integral part (indeed the specific beginning) of either the first or subsequent attacks. Other factors, however, will provoke attacks: tonsillectomy, severe injuries, injections of typhoid vaccine, or an abdominal or other operation²⁰⁰. Bland and Jones¹⁷⁹ noted an initial, generally a subsequent, attack after tonsillectomy, appendectomy, or arthrodesis. Intravenous injections of typhoid bacilli have been used in the treatment of the disease. To study the effect, Bland and Jones gave a total of 12 such injections to 10 patients. In six cases an exacerbation appeared immediately or within three weeks. In two cases there was a doubtful, in four no, reaction. No serious effects were noted. Following the reactions "there seemed to be a more rapid progression to quiescent rheumatic fever than was previously noted." Studying the immunity mechanism, Coburn and Pauli¹⁷⁸ performed splenectomy on 20 children with quiescent rheumatic fever, in nine of these 20 cases recrudescences developed as a direct sequel to splenectomy, none died.

Effect of Pregnancy With others Willius²⁰¹ believed that in many cases of rheumatic carditis the stresses of the latter months of pregnancy, of actual labor and those incident to the subsequent physical care of the infant may precipitate cardiac decompensation. However, trouble does not always develop. Of 38 rheumatic women seen by Brenner¹⁶⁰ 15 had no trouble with repeated pregnancies up to 10. Four had no trouble with one or more early pregnancies, but heart failure developed after later pregnancies. In 19 cases heart failure began or became worse in the first pregnancy, four patients died within a few weeks of delivery.

Evidences of Activity or Reactivity The following are considered evidences of activity of the disease: the usual clinical evidence of slight persistent fever, tachycardia, joint pains, nodules, persistent underweight, pallor, unexplained abdominal pain, nosebleeds, tendency to vomit, leukocytosis, lassitude, an increased sedimentation rate, and electrocardiographic alterations.^{164, 176, 202-203} The disease may be active, however, without fever. If in the absence of fever the sleeping pulse rate is about the same as "the alert rate" (when the child is awake), activity can generally be presumed. A recrudescence is often evidenced by gradual quickening of both sleeping and alert pulse rates. On the other hand, if a drop of 10 to 20 beats per minute during sleep is noted, a rapid alert rate is probably of nervous origin.¹⁷⁶

Recurrences Of Shapiro's¹⁶⁴ 342 patients, 52 per cent had only one attack within the period of study (12 years or less), 48 per cent had one or more recurrences. Of the latter, 27 per cent had them within one year, 54 per cent within two years, 70 per cent within three years, and practically all within nine years. Of Gilkey's¹⁶⁹ 458 patients, 49 per cent had recurrences within three years. Of Preston's¹⁶⁶ 157 patients with carditis 30 per cent had one attack only, 38 per cent had one relapse, 32 per cent had two or more relapses. Of those without carditis, 70 per cent had one attack, 24 per cent had one relapse, 6 per cent two or more.

End Results The course of rheumatic carditis has been outlined by De Giuff and Lingg¹⁷² who studied 644 patients who died of it. Fifty-six per cent were males, 44 per cent females. Rheumatic carditis usually existed alone (95 per cent of cases), was seldom combined with other etiologic types (5 per cent). The average patient is infected at the age of 17 years, but will be free of symptoms and able to carry on ordinary physical activity for 11 years. He will then begin to suffer from diminished cardiac reserve, culminating in heart failure two years later. From this time until his death, three years later, he is wholly an invalid, or at least in most cases is seriously incapacitated. The period of economic usefulness of a rheumatic victim is generally less than nine, not more than 11, years after the initial rheumatic infection. Once symptoms of cardiac insufficiency appear, heart failure and death rapidly ensue. Fifty per cent suffer their first symptoms and failure and die within a period of from 16 to 20 years after initial infection (or

between 20 and 40 years of age) To see even terminal stages of the disease in patients more than 50 years of age is uncommon Death usually occurs from heart failure, but life is shortened in some cases by subacute bacterial endocarditis, pneumonia and other diseases Of the 644 patients in De Graff and Lingg's series, 43 per cent developed auricular fibrillation, but this did not per se determine prognosis on life expectancy When fibrillation, a late manifestation, set in, the die was already cast The incidence of the various valvular lesions was given Mitral disease was more frequent in women, aortic disease in men The location or number of valves affected did not seem to influence the duration of life except in the case of pulmonic or tricuspid valves then the prognosis was less favorable

A similar study of 113 cases was made by Davis and Weiss¹⁷¹ After the onset of the disease, the patients lived from a few weeks to 40 years About 50 per cent lived less than six years about 50 per cent lived from six to 25 years

Etiology and Pathogenesis Arguments on various theories are essentially similar to those reported in previous Reviews

Infectious Theory Evidence supporting this theory is direct and indirect Presumably direct evidence is that from cultures of the blood, nasopharynx and other tissues Blood cultures by McIntosh and Wood¹⁷⁰ were negative in six cases, positive for non-hemolytic streptococci in one As already noted, the frequency with which tonsillar or upper respiratory infection occurs as a precursor of rheumatic fever has again been demonstrated by Coburn and Paul,¹⁷⁸ Gilkey¹⁶⁹ and McIntosh and Wood¹⁷⁰ The significance of this prodromal infection is debated In Bland and Jones' series¹⁷⁹ of "over 1,200" rheumatic children and adolescents, respiratory infections were experienced by 75 per cent of those with recurrences However, many exacerbations occurred without preceding respiratory infections and recurrences were frequently precipitated by other and nonspecific factors such as accidents, abdominal operations, or injections of typhoid vaccine Bland and Jones therefore concluded that the bacteria causing respiratory infections may not be as specifically related to the disease as some believed, but may be of secondary importance

Of rheumatic attacks among 222 patients of Wheeler, Ingerman, DuBois and Spock¹⁸⁰ less than 10 per cent were preceded within three weeks by a respiratory infection When such infections did develop, only 16 per cent of them produced rheumatic activity Practically all of another group of 123 patients suffered respiratory attacks on an average of five each Although 54 per cent of these infections were with hemolytic streptococci, 84 per cent were not associated with rheumatic activation A comparison of 4867 throat cultures from 123 rheumatic, and of 1231 cultures from 109 nonrheumatic, children by Wheeler, Wilson and Leask²⁰⁴ showed no significant difference in the frequency or in the appearance time of hemolytic streptococci and no noteworthy difference in the incidence of such organisms

in throats during apparent health, upper respiratory infections or rheumatic activity. These authors concluded that an etiologic relationship between rheumatic fever and respiratory infections with hemolytic streptococci was not evident.

This conclusion is at variance with that of Coburn and Pauli¹⁷⁸ who distinguished between respiratory infections with non-toxin producing hemolytic streptococci, ineffective in provoking rheumatic exacerbations, and those with a strong, skin toxin-producing hemolytic streptococcus capable of activating rheumatic processes. In the winter of 1934, the throats of a group of rheumatic children were infected with the former type—a non-toxin producer—in none did an exacerbation develop, nor did any during a subsequent influenzal epidemic. Soon thereafter these same children were exposed to an epidemic of a toxin-producing hemolytic streptococcus of a single type. Of 16 rheumatic children thus affected, 14 had acute rheumatism, two escaped. The 14 affected patients developed increased antistreptolysins with the onset of symptoms. The two who were definitely infected with the same toxin-producer but escaped a rheumatic exacerbation did not develop antibody (antistreptolysin) response. Seven rheumatic children did not contract the toxin-producing streptococcal infection, thus indicating that some susceptible persons may live in close association with an epidemic of acute rheumatism, develop no rise in antistreptolysins and maintain excellent health. An additional patient, one with congenital heart disease, did become infected with the “effective strain” and did develop a typical antibody response, yet this patient escaped rheumatic manifestations, indicating that more than a bacterium is responsible for the disease. Cultural characteristics of the effective and non-effective strains were essentially similar, but the effective strain was capable of producing strong skin toxins and streptolysins and was indistinguishable from scarlatinal strains of hemolytic streptococci.

Indirect evidence for the infectious theory is derived from skin tests, and tests for streptococcal agglutinins, antistreptolysins, streptococcal complement, antistreptolysins and precipitins. *Skin tests* with hemolytic streptococci were “positive” in 80 per cent of Gilkey’s¹⁶⁹ 458 rheumatic children and in 20 per cent of controls, and in 75 per cent of Kaiser and Keith’s²⁰⁰ 200 rheumatic children and in 32 per cent of their non-rheumatics. They were also positive, however, in a fairly high percentage of patients with other streptococcal infections.

Agglutinins Blair and Hallman²⁰⁰ found a somewhat larger percentage of high agglutinin titers with serums from cases of rheumatic fever than has been reported by others. Twenty-five serums from 24 patients were tested agglutinins to Cecil’s typical strains of hemolytic streptococci AB 66 (from a patient with atrophic arthritis) and Q 33 (from a patient with rheumatic fever) were found in dilutions of 1:160 or more in 14 serums. Only one patient with rheumatic fever had agglutinins (1:40) to *Streptococcus viridans*.

The *streptococcal complement-fixation test* was positive in varying degrees in Coburn and Pauli's active cases of rheumatic fever (1932), but was only occasionally positive (sometimes strongly) in quiescent cases. Beck and Coste²⁰⁷ found the test positive for only seven of 79 patients with various types of rheumatism or arthritis, presumably streptococcal. It was positive in two of four cases of rheumatic fever, but also often positive in cases of pregnancy and of tuberculosis.

Antifibrinolysins Broth cultures of hemolytic streptococci (but not of other organisms) of human origin rapidly liquefy the fibrin clot of normal human plasma. In patients convalescent from acute hemolytic streptococcal infections (and rheumatic fever) the fibrin clot is highly resistant to this fibrin-lysis owing to the presence of a substance (antibody) called "antifibrinolysin." Although certain amounts of antifibrinolysin are found in the plasma of normal persons and those without evidence of recent hemolytic streptococcal infection, Myers, Keefer and Holmes²⁰⁸ found much greater amounts in plasma of patients with erysipelas and other acute hemolytic streptococcal infections and with rheumatic fever. (However, antifibrinolysins were not found in cases of atrophic arthritis—Ed.)

Precipitins Extending previous work (Coburn and Pauli, 1932, Schlesinger and Signy, 1933) Schlesinger, Signy and Payne²⁰⁹ demonstrated precipitins to hemolytic streptococci in the blood of non-rheumatic patients with recent tonsillitis, but in greater amounts in that of rheumatics. Precipitins are practically absent in cases of quiescent rheumatic fever, in rheumatic patients, they generally appear between the tenth to thirtieth day after the acute throat infection. Just at this time rheumatic relapses commence. Apparently when immune responses are at their height, the patient's tissues seem to possess a vulnerability that perhaps allows an as yet undiscovered cause of rheumatic fever, perhaps a virus, to enter the body or, having already entered, to become active.

Antistreptolysins * The normal level of antistreptolysins is from about 50 units¹⁷⁸ to 100 units²⁰⁶. Blair and Hallman²⁰⁶ found increased antistreptolysins in 15 of 18 rheumatic patients. The disease was "inactive" in the three whose titers were normal. Coburn and Pauli¹⁷⁸ found a marked increase in antistreptolysins (to an average of about 500 units) in rheumatic patients infected by the "effective strain" of hemolytic streptococcus, the increase was coincident with onset of symptoms of rheumatic activity. Unless such a rise appeared, no rheumatic exacerbation was experienced. Apropos of the reported rarity of rheumatic fever in the South as compared to the North, Coburn and Pauli²¹⁰ found that high antistreptolysin titers are more prevalent in latitudes over 40° than in those below 35°. However,

* Coburn, Wilson and their colleagues use the terms "antihemolysin" and "antistreptolysin" synonymously, but prefer the term "antistreptolysin" which emphasizes the relation of the antibody to streptococci.²¹² To be absolutely correct one should use the term "antistreptohemolysin." The antigen, streptolysin, is a soluble product of hemolytic streptococci which hemolyzes erythrocytes. The antibody, antistreptohemolysin or "antistreptolysin," neutralizes the antigen streptolysin, one titrates with streptolysin to determine the presence and titer of "antistreptolysin"—Ed.

the work of these investigators is again at variance with that of their fellow townsmen, Wilson, Wheeler and Leask²¹¹ The latter made clinical, bacteriologic and immunologic studies on 80 rheumatic subjects over a period of 12 to 18 months The average antistreptolysin value was 135 units for those with inactive disease, the range was 25 to 715 units The range among patients with inactive or active rheumatism or with respiratory infections was about the same Those with respiratory infections unassociated with hemolytic streptococci showed a higher average titer and a greater rise than those with hemolytic streptococcal respiratory infections An increased titer therefore does not necessarily indicate a hemolytic streptococcal infection Rheumatic activity developed in many cases without preliminary respiratory infection two-thirds of them had no rise in antistreptolysin titer A rise in antistreptolysins is therefore not a necessary accompaniment of rheumatic fever Increased antistreptolysins seemed directly related to the extent of the local and constitutional symptoms of the respiratory infection, irrespective of the presence of hemolytic streptococci and bore no relation to the clinical course of rheumatic activity

Interpretation of Immunologic Data (The work of the Columbia group seems to be in sharp contrast with that of the Cornell group The writings of the former seem to us easier to follow, although the work of both groups appears to have been done very carefully and exhaustively It was impossible for us to interpret these immune responses or to harmonize the conflicting views In an attempt to do so the editors wrote Drs Wilson, Coburn and Pauli A possible explanation was offered by Dr Wilson She and her colleagues included non-rheumatic children among their controls Coburn and Pauli apparently did not Antistreptolysin values for babies approximate those for adults, but those for children may not Because children are so susceptible to respiratory infections they may, even after minimal infections, have values higher than adults or babies Rheumatic fever in childhood may be an entity not entirely comparable to that in adults A further factor may have been the selection of cases for study there may have been less selection of those of Wilson and her colleagues who included records of all cases seen in a specified time Since high antistreptolysin titers were noted in patients who did not develop rheumatic exacerbations Wilson was inclined to doubt the importance of a special, potent strain of hemolytic streptococcus Obviously, final interpretation must await more data thereon However, the preliminary interpretation of Coburn and Pauli¹⁷⁶ is given—Ed)

Three factors seem to be necessary for the production of a rheumatic attack (1) infection, not just with any hemolytic streptococcus but with a highly effective agent—a strong soluble-toxin producing hemolytic streptococcus, (2) a disease pattern peculiar to each rheumatic subject, (3) an intense immune response as indicated by a rise in antistreptolysins A patient can be infected with an "effective strain," but unless a marked antibody response develops, a rheumatic exacerbation does not ensue Therefore, the character of the antibody response plays a large part in determining whether an attack will follow If the patient's antibody-producing tissue is quiescent when the hemolytic streptococci or other precipitating agent acts (for example, an operation such as splenectomy), no rheumatic exacerbation ensues If the antibody-producing tissue is in a state of activity at that

time, an exacerbation may result (To this extent, then, the patient is as much, if not more, the cause of the disease than the invading substance—Ed) Thus the pathogenesis of rheumatic fever is presumably as follows (1) the toxin-producing hemolytic streptococcus initiates a process peculiar to rheumatic subjects, (2) in the course of the process a substance is released presumably from the antibody-producing tissues, which directly or indirectly alters mesodermal structures, this substance is probably not the infecting organism, and at present there is no evidence to suggest that it is viable, and (3) the release of this toxic substance seems to occur only when there is an immune response to hemolytic streptococci

Coburn and Paul's idea of a more or less specific sensitivity or allergy, a peculiar antigen-antibody reaction involving a special type of hemolytic streptococcus, is in contrast with that of Swift²⁰ and others that rheumatic fever results from a hypersensitivity to a wide range of streptococci or other bacteria. The idea of a broad streptococcal allergy is accepted by many^{1,9,160,213,214,215}. In support of the allergic theory various tissue reactions, including some resembling those of rheumatic fever, were produced by Chiari¹⁸² in animals given allyl-formiate, by Baker, Thomas and Penick²¹⁶ in animals sensitized to beta hemolytic streptococci, and by Andrieu and Ravennà²¹⁷ in animals sensitized to arthrotropic streptococci. However, not all of the animals presented these reactions, and many of the reactions were considered quite nonspecific, unlike the lesions of rheumatic fever.

Objections to the idea that the disease represents general allergy have been raised by Stuart-Harris²¹⁸ and by Sayle²¹⁹. Objections are that (1) the percentage of skin reactions to hemolytic streptococci is no greater in rheumatic than in control groups, and is much less than in scarlet fever, (2) skin reactions to non-hemolytic streptococci are present in rheumatic fever but also in controls, (3) there are many diseases due to hemolytic streptococci and other organisms, to which candidates for rheumatic fever should be sensitive, which are not associated with rheumatic-like manifestations, (4) certain "skin-positive rheumatic patients" with hemolytic streptococci in their throats escape relapses, and (5) in artificial sensitization, the silent period between resensitization and symptoms becomes less and less, in rheumatic fever it remains about the same in spite of repeated exacerbations.

The frankest objections are those of Freeman,²²⁰ who criticized the whole idea of bacterial allergy in rheumatism, particularly the chronic types. In the first place "allergy" is at present a non-definable term, even authorities being troubled by its ambiguity and the difficulty of using it with precision. The types of streptococci, the germs presumably most concerned with bacterial allergy in rheumatism, are not yet satisfactorily classified. Skin tests afford little or no assistance and are quite inadmissible as evidence for "allergy" because their results are so inconclusive. In rheumatism the reactions vary greatly in intensity and time of appearance (four hours to four

days) They do not appear after five to 10 minutes as do the characteristic "wheal" reactions of "allergic diseases" like hay fever. Reactions may also occur in non-rheumatic persons and are not characteristic either of the disease under study or even of the organisms used therefor. Various immunologic reactions reported are not clear-cut because the antigenic properties of the responsible streptococci are adaptable, not fixed. One must strictly differentiate between (1) a specific infectious disease with allergic phenomena (as in tuberculosis), and (2) an "allergic disease" of the sort usually characterized by paroxysmal attacks, as in asthma, hay fever, etc. Aschoff would say, allergic phenomena are present in rheumatism, but rheumatism is not an allergic disease. This does not help us, however, to understand rheumatism. "The use of the word, 'allergy' will help only in so far as it emphasizes the action of the dissolved products of invading microorganisms (rather than the whole organism itself) and the necessity for immunization and desensitization."

We are inclined to believe that so beautiful a word as allergy must mean something important without concerning ourselves too much as to what that something may be. We are working in a fog and have as yet no clear vision. The word allergy is, to my mind, not a gleam of sunshine breaking through, but an extra wisp of fog."

Virus Theory In some ways rheumatic fever resembles a virus disease (Sayle²¹⁹). In certain diseases the virus apparently enters the body via the nasopharynx, a nasopharyngitis precedes rheumatic fever. Some virus diseases predispose to recurrences, which is the case in rheumatic fever. Virus diseases generally have a long incubation period (nine to 24 days), the "silent period" in rheumatic fever is about 10 to 21 days. Viruses are difficult to grow and are generally ultramicroscopic, were a virus responsible for rheumatic fever, current failures to grow or see it could be explained. In some virus diseases intracellular inclusion bodies are demonstrable, they have not been found in rheumatic fever, although granules of an unknown nature have been found within tissues by certain stains.

Schlesinger, Signy and Amies²²¹ isolated from the pericardial fluid of seven patients and from the pleural exudate of one patient particles which resembled virus elementary bodies. Suspensions of these bodies were specifically agglutinated by serums of patients with active rheumatic fever, but were not agglutinated by that of normals or of patients with inactive rheumatic fever or with various non-rheumatic infections. Coles²²² recovered similar "virus-like bodies" from pericardium and pericardial exudate of a victim of rheumatic fever (also from synovial fluid in four cases of atrophic arthritis).

(Proof of the significance of these bodies lies in the reproduction of the disease when they are injected into animals. This has not been done by any of these workers.—Ed.)

Theory of Nonspecific Infection Plus Vitamin C Deficiency Supplementing work with Mettliher and Connor (1934), Rinehart²²³ presented fur-

ther work in support of his idea that rheumatic fever may be the result of the combined influence of deficiency in vitamin C and infection. In guinea-pigs on a diet devoid of vitamin C which were inoculated with a guinea-pig strain of hemolytic streptococcus or other organisms, cardiac and articular lesions, and occasionally subcutaneous nodules, notably resembling those of rheumatic fever, developed with considerable frequency. Guinea-pigs infected with these organisms but on an adequate diet did not show such lesions, and those treated with a deficient diet alone showed only slight lesions. Swift²⁹ agreed that lesions of some sort were thus experimentally produced, but thought they were scorbutic, not rheumatic. He and his colleagues²²⁴ found no difference between rheumatic and non-rheumatic patients in the metabolism of vitamin C. Patients with active and quiescent rheumatic fever were treated with cevitic acid (concentrated vitamin C). The course of the disease was uninfluenced. Faulkner²²⁵ also noted no definite effect from feeding a high-vitamin C diet in 27 cases of rheumatic fever.

Perry²²⁶ applied the Harris-Ray test for vitamin C deficiency (urinary excretion of ascorbic acid after the administration of a test dose of vitamin C) to five patients with active and six with quiescent rheumatic carditis. Two of the former and three of the latter gave evidences of a mild vitamin C deficiency. However, the capillary resistance test was normal in all five. It was concluded that mild degrees of vitamin C deficiency are not uncommon in rheumatic children but are not important in the etiology of acute rheumatism.

Warner, Winterton and Clark¹⁶⁸ found a much higher consumption of fresh fruits and vegetables by rheumatic children and their families than by children in institutions in which there was a very low incidence of rheumatism. Although the consumption of animal protein and dairy products was low and that of carbohydrates high in the rheumatic group, no one dietary factor could be found as a contributory cause for the disease. Extra feedings with vitamins A and D proved of little value.

Treatment—For the general disease. Ritchie¹⁵⁹ ascribed no curative value to any serum, vaccine or medicine, including salicylates. The majority ascribe to salicylates only an analgesic effect, and no power to prevent or modify carditis. Citing reports on their ineffectiveness in preventing carditis and on their occasional toxic effects, Apfel²²⁷ stated that the use of salicylates is continued "simply because it has been handed down to us and we don't know what better to use." That salicylates are a specific is a "pernicious doctrine," according to Eason²²⁸ who considers doses now used sometimes dangerous. Others do not approve "the current fashion of belittling the use of salicylates." Antell¹⁸⁴ still regards them as "the sheet anchor" of treatment, even if they are not specific and are only analgesic. He prescribes them in large, "almost toxic" doses for children, 60 to 120 grains in 24 hours with sodium bicarbonate. Taussig²⁰² prefers aspirin.

to sodium salicylates, considers 30 to 45 grains daily sufficient, and 10 grains of salicylate per 10 pounds of body weight as a maximal daily dose for most children. Wilkinson¹⁶⁷ and Lyon^{174, 175} believed that inadequate doses are generally given and that, when enough is used, the drug does definitely prevent or modify the carditis in some cases. To prevent acidosis Lyon prefers "salicionol," an alkalized salicylate.

Replacing salicylates, amidopyrine is favored by Apfel,²²⁷ neocinchophen (tolysin) by Poynton.²²⁹ Fraser²¹⁰ saw an instance of fatal cinchophen poisoning in a case of rheumatic fever. Slocumb⁹⁹ reported the use by Frazer and Walsh²³¹ of intravenous injections of olive oil, reduction of fever and "adsorption of toxins by the minute fat globules" were presumably obtained. (Laboratory studies had not yet been carried out. The work has not been fully reported—Ed.) With similar intent St. Jacques²³² gave colloidal charcoal intravenously. (The data are very meager. No conclusions can be drawn—Ed.) When the hemoglobin fell below 50 per cent, Lyon^{174, 175} gave periodic transfusions of 100 to 200 c c of blood.

Extra vitamin C was given by Rinehart²⁻³ who was encouraged by preliminary results. However, no specific effect from vitamin C (530 c c of orange juice, or 200 to 300 mg in crystalline form) daily for four weeks was noted by Faulkner.²²⁵ The use of vitamins A and D "radiostoleum" appeared of little value to others.¹⁶⁸

Tonsillectomy Opinions on the value of tonsillectomy still differ. The majority favor early tonsillectomy if the tonsils are definitely diseased, but believe it should be done only when the disease is relatively inactive.^{159, 160, 167, 169, 203, 227, 229, 233} otherwise, an exacerbation may be precipitated. If the disease's activity is unusually persistent, tonsillectomy may have to be done while activity is present. (According to Robey, 1932, tonsillectomy even during activity of the disease can generally be done with safety and may be necessary if such activity is prolonged—Ed.) As a prophylactic Lyon¹⁷⁵ advised salicylate therapy for 10 days before and after tonsillectomy. Some favor tonsillectomy on suspicion in all cases, even when tonsils are not obviously infected. Tonsillectomy does not prevent rheumatic fever, which may result from pharyngitis in a tonsillectomized child, but a clean throat will diminish a predisposition to upper respiratory infections. According to the large statistics of Kaiser,²⁹ the child who has had his tonsils out is less likely to have rheumatic manifestations, and if he does have them serious cardiac complications are less likely to develop. Although the incidence of recurrent attacks was not influenced by tonsillectomy, the mortality among 600 children was about twice as high in those who had tonsils at the time of the initial attack as in those whose tonsils had been removed. Gilkey¹⁶⁹ likewise found a 50 per cent lower mortality rate among those whose tonsils were out before the first attack. Preston,¹⁶⁶ however, found only a slight advantage for the tonsillectomized child.

Vaccines, Antitoxin Attempts at desensitization by streptococcal vac-

cines and filtriates seemed worth-while to some,^{169 207} useless to others¹⁷⁶ Streptococcal antitoxin (scarlatina) was used by Eason²²⁸ in 37 cases, in 73 per cent "complete recovery" ensued after the use of 30 c c twice, 36 hours apart. Further doses had to be given to 27 per cent of the patients. Improvement began within 24 hours of the two initial doses. A brief febrile reaction usually preceded improvement. Serum rash and fever for one to two days later appeared in 32 cases. One patient died probably from a serum effect. Two of three control patients treated with normal horse serum also recovered. Because a few of the patients were relieved without developing febrile reactions, Eason believed that results were not entirely due to a foreign protein effect. No conclusions on the prevention of carditis were given.

(The use of three controls was insufficient. Foreign protein reactions may not need to be febrile to be effective. To date we would conclude that this "antitoxin method" gave nonspecific results, due to a foreign protein reaction—Ed.)

Using scarlatinal toxin Coburn and Pauli¹⁷⁸ attempted active immunization of 113 normal persons. Skin reactions to streptococcal toxin were markedly diminished thereby, but there was no evidence that this treatment increased resistance to streptococcal infections or prevented rheumatic fever. Ten patients with quiescent rheumatic disease were given "passive immunization" with antitoxin (antistreptococcal serum). The introduction of these protective antibodies just prior to an expected attack (just after a streptococcal infection) did not decrease, and possibly increased, the intensity of the rheumatic recrudescence.

Fever Therapy with Typhoid Vaccine or Radiant Energy Typhoid vaccine intravenously should be tried when salicylates fail, according to Cecil²³⁴, acute febrile polyarthritis may be thereby aborted. Although reactions to such vaccine, given when the disease is relatively inactive, may provoke a mild exacerbation, the disease thereafter may become more rapidly quiescent, according to Bland and Jones¹⁷⁹.

Fever therapy was given by Sutton and Dodge²³⁵ to 18 patients with active carditis. In 16 (who also had chorea) fever was produced by typhoid vaccine reactions, in two by radiant energy. From four to 14 fever sessions were given over a period of five to 26 days. In all cases clinical signs of activity of carditis completely subsided within 10 to 14 days after treatment. However, in some cases, relapses occurred after several months. The conclusions were that such fever therapy did not harm patients with sub-acute or inactive rheumatic carditis, it seemed to benefit them and deserved further study.

(The period of observation, about two years, was too short to permit final conclusions on the permanency of the effect. Further study is also required to confirm the apparently good immediate effects—Ed.)

Splenectomy did not favorably modify the course of the disease¹⁷⁸

For Joints Rest and salicylates continue as standard therapy Splints properly applied are far superior to salicylates (Apfel²²⁷)

For the Heart There are three objectives (1) immediate relief of symptoms, (2) restitution of cardiac reserve to the greatest degree possible, and (3) maintenance of cardiac efficiency after the patient is up and about by a carefully planned and individualized regimen Indications for digitalis, quinine, and salyrgan or other diuretics have again been given^{174, 175, 200-202} The minutiae of a "cardiac regimen" are clearly set forth in several short readable papers which particularized the time for renewal of activity of the convalescent patient, the plan of graded activity and the method for recognizing the changing functional status of the heart^{176, 200, 202, 236} The physiologic effect of light muscle training was carefully studied by Proger and Korth²³⁷ The establishment of convalescent "hospital-schools" and cardiac camps has made much more effective the care of convalescent children^{176 238}

To lessen cardiac strain and to prevent disaster in cases in which patients become pregnant, cesarian section under local or spinal anesthesia,²⁰¹ or induction of premature labor,¹⁶⁰ may be indicated

For pericardial effusions Antell¹⁸¹ preferred the use of oxygen tents for two to four days rather than paracentesis

Prophylaxis The prevention of the initial attack as well as of exacerbations depends at present on the fullest maintenance of a "physiologic life"¹⁵⁹ This necessitates the education of civic authorities to the value of smokeless, sunny cities with no overcrowding and with well-built homes, and the education of parents in "the wise nurture of children" with high resistance to disease—the prescription for which is good food, a proper ratio of rest and exercise, sunshine, frequent baths with contrast douches, the use of porous, light warm clothing, the removal of infected foci, and above all, the avoidance of respiratory infections by shunning crowds in unseasonable weather, and perhaps by the use of vaccines for children with repeated colds^{167, 203 239} Particularly desirable for children are long stays in semi-tropical or tropical climates

SYDENHAM'S CHOREA

Chorea may occur alone or with other manifestations of rheumatic fever, chiefly arthritis and endocarditis Some consider it a disease in itself, others regard it as a symptom of rheumatic fever^{240, 241} Still others believe it may be a symptom of several diseases²⁴² The close relationship of chorea and rheumatic fever is often very apparent Considering chorea a single manifestation of rheumatic fever, Jones and Bland (Boston)²⁴¹ found that of 1000 cases of rheumatic fever, nearly 50 per cent (482) had frank chorea, the rest had other symptoms of rheumatic fever without chorea Of the 482 that had chorea, 28 per cent had chorea alone, 72 per cent also had other symptoms of rheumatic fever In the South chorea is rare Of 224 pa-

tients with rheumatic carditis in Dallas, Texas, only four had chorea¹⁷⁸ Choreia is considered a "white man's disease," rare in American Indians and negroes²¹³ and in the tropics. However, Kutumbiah¹⁶³ and Wig¹⁶² noted several typical cases in India.

If chorea is a separate disease from rheumatic fever, according to Schwartz and Leader²¹⁰ one should expect the end of choreiform motions to signify the end of the disease, but if it is part of rheumatic fever, one may expect proof in the form of associated or subsequent carditis. Because in practically all of their 75 cases of "pure chorea" (no history and no evidence of rheumatic fever) carditis (myocarditis and mitral valvulitis) eventually developed within seven to eight years, Schwartz and Leader concluded that chorea is a symptom of rheumatic fever and that here also "the heart is always involved." In most cases the carditis developed insidiously, often without other attacks of chorea. In no case did aortic valvulitis, pericarditis or subcutaneous nodules develop.

These findings are in sharp disagreement with those of Jones and Bland²⁴¹. Carditis developed in only 3 per cent of 134 cases of "pure chorea," those without other symptoms of rheumatic fever, the mortality was 0.7 per cent. In contrast, carditis developed in 86 per cent of 518 cases of rheumatic fever without chorea, the mortality was 32 per cent. It developed in 80 per cent of 184 cases of chorea which preceded other evidences of rheumatic fever, and in 60 per cent of 164 cases of chorea which followed other symptoms of rheumatic fever. The presence or number of attacks of chorea apparently did not influence the development of carditis. Thus Jones and Bland regarded "pure chorea" as a mild manifestation of rheumatic fever, one of good prognostic import but one in itself not especially conducive to carditis.

From a study of 150 cases Geistley, Wile, Falstein and Gayle²⁴² concluded that chorea is not a disease but a symptom, more frequently of psychic trauma than of rheumatism. In their cases little relation to previous infection was found and no clinical evidence (no fever, leukocytosis, or increased sedimentation rate) of acute infection. Only 12 patients showed persistent signs of carditis. That other insults than rheumatism can cause chorea is also the suggestion of Hewins²⁴⁴ who noted a case with neurosyphilis, of Lewis and Minski²⁴⁵ who noted four cases with psychoses, and of Brian and Gerundo²⁴⁶ who noted a fatal case of chorea gravidarum and concluded that, in pregnancy, one may encounter the Sydenham (rheumatic) variety or another type, a symptom of toxemia of pregnancy.

Treatment Usual recommendations are rest and quiet, good nursing, sedatives, salicylates, pyramidon, arsenic or stramonium, but, unaffected thereby, the disease may run its usual course of six to 10 weeks or longer²³⁸^{243, 247}. Jones²⁴⁷ found streptococcal vaccine valueless. Small's antiserum (1927) helped only 13 per cent of Wetchler's²⁴³ patients.

Tonsillectomy Jones²⁴⁷ considered tonsillectomy indicated in cases of

choira with other rheumatic symptoms, but not particularly in "pure chorea." It should be done only when the disease is quiescent. Tonsillectomy has no effect on the course, duration or tendency to recurrences of chorea, but the tonsillectomized patient with chorea is much less likely to have endocarditis.²¹²

Nirvanol Results from nirvanol were satisfactory to Wetchler,²¹³ who had no complete failures in 115 cases. The disease was generally terminated within three weeks, although recurrences were not prevented. The plan of treatment and the "nirvanol reaction" were described and a brief review of the literature was given. Twenty-one moderately severe and five severe cases were treated by Bender and Pratt²¹⁶ with good results. Two patients had recurrences within a year. No harmful effects and no fatalities were encountered. Jones²¹⁷ used nirvanol in three cases, one patient had no febrile reaction and obtained no relief, another was unrelieved and a "very serious, almost fatal reaction with suppression of bone marrow" developed. Jones considered it a dangerous drug and its use unjustified.

Fever Therapy Some believe that the results with nirvanol and other fever-producing substances are due to the fever. Jones²¹⁷ used typhoid vaccine for fever therapy, his results (not fully reported) were not striking. The results of Sutton and Dodge (1933) with typhoid-vaccine fever reactions, however, were very striking, attacks were thereby shortened by an average of 36 days as compared with results when physical therapy, drugs, and diets were used. The average duration of attacks of 150 patients treated by vaccine reactions was 8.5 days, that of 150 patients treated otherwise 42.6 days. Sutton and Dodge^{220, 219} recently noted similarly good results with "artificial fever." Foreign protein shock is avoided, fever is controllable, and only one or two sessions (105° to 106° F. for five hours) instead of several daily reactions are necessary. Associated active carditis was not aggravated, indeed seemed to be benefited thereby.

Desjardins and Popp^{10, 72} considered artificial fever therapy most effective. All of nine children "improved satisfactorily." Daily fever sessions, at 103° to 104° F. for three to four hours, were given for one week. "In a week's time the attacks had passed." Two patients with chronic chorea treated by Hefke^{40, 51} were "improved," and of seven previously treated unsuccessfully with typhoid vaccine, six were controlled by artificial fever given by Schmidt.⁴⁵ Nine of 12 children treated by Schnable and Fetter⁷² were "cured" after an average of four fever sessions and had no recurrences within several months. Two children treated with low temperatures were only partially relieved. One child died 17 hours after collapsing during the first partial fever session as a result of a disturbance of the heat-regulating mechanism. In spite of this they regard fever therapy as offering the best chance of cure. (For comments on the general safety of fever therapy, the avoidance of unfavorable reactions and the probable inevitability of an occasional fatal reaction, the reader is referred to the discussion on fever therapy under "Treatment of gonorrheal arthritis"—Ed.)

CHRONIC ARTHRITIS

Incidence More statistics on the incidence and types of arthritis seen in general practice are needed. More available are statistics on the relative incidence of different types of arthritis seen in special clinics. Of 400 consecutive patients with "chronic arthritis" at the arthritis clinic of the Presbyterian Hospital, New York, 75 per cent had atrophic or hypertrophic arthritis³⁴. Of 200 consecutive patients with acute or chronic "rheumatic diseases" seen at The Mayo Clinic, 65 had atrophic arthritis, 39 hypertrophic arthritis, 30 had both types and 66 had other types of arthritis¹⁰⁶. Of Lang's²⁵⁰ 100 patients with chronic arthritis 47 per cent had atrophic, 21 per cent hypertrophic arthritis, 28 per cent had both types (and 4 per cent other types of arthritis?—Ed). Of Gray's²⁵¹ patients with chronic arthritis 70 per cent had atrophic, 30 per cent hypertrophic arthritis.

General Remarks on Etiology and Relationship of the Two Great Types There are four different opinions on the relationship between atrophic and hypertrophic arthritis: (1) that they are quite separate diseases of different etiology, the opinion of the majority^{11, 252}, (2) that the two types should be regarded as separate clinical entities, but may well have a common (but variable) etiology²⁵³, (3) that the two types are variants of one disease, caused by any one of a number of agents, and (4) that the two types are manifestations of one disease and have a single etiology. Thus both types were ascribed to "cold edema" by Bjorkman,²⁵⁴ to a sulphur deficiency, particularly of cartilages by Wheeldon²⁵⁵.

Distinctions Between the Two Great Types Clinical distinctions remain as previously reported^{1, 2}. Pathologic distinctions between the two types were again described by Parker and Keefer²⁵⁶ who insisted that the gross and histologic features of each are quite different even when both coexist in the same case. They therefore regarded as untenable the idea that both may result from the same underlying factors.

Roentgenographic alterations which appear as each type progresses were again reviewed by Doub¹¹ and by Ferguson, Kasabach and Taylor,²⁹ who analyzed 49 roentgenographic characteristics. Since varieties of bone atrophy, pitting and zones of erosion are common to the roentgenograms of many different types of arthritis (atrophic, hypertrophic, gouty, gonorrheal, tuberculous and others), it is agreed that there is no one pathognomonic feature in any one type. Each, however, has its characteristic picture or combination of alterations which may make the roentgenogram in a given case highly suggestive. These alterations, best seen in roentgenograms of hands, feet and knees, are as previously reported^{1, 2}.

(Roentgenographic features of each type have been described in numerous reports. Studies now much more to be desired are those on serial roentgenograms of the different arthritides—consecutive pictures taken of the same patients from the onset to the inactive stage of the disease. Such data, now very meager, are needed to determine the natural course of the disease and to establish the average and the minimal and maximal time that elapses between the disease's onset and the appearance

of each of the various roentgenographic abnormalities. Among the practical questions thus answered would be: How long must a roentgenogram of a painful joint remain "negative" before one can conclude that the disease in a given case is periarticular, not intra-articular, and probably represents periarticular fibrositis and not a mild slowly progressive atrophic arthritis?—Ed.)

Chemical differences between the two types of arthritis have been noted by several^{29, 31, 257-260} and are as follows. In atrophic arthritis the sedimentation rate is usually more than 30 mm. in one hour; agglutinins to hemolytic streptococci are usually present in high titer. There is an increase in plasma fibrinogen and globulin fraction, a fall in the albumin fraction, and the albumin-globulin ratio is frequently less than 1. Serum calcium is essentially normal and the plasma cholesterol tends to be decreased. In hypertrophic arthritis the sedimentation rate is rarely more than 20 to 30 mm., agglutinins to hemolytic streptococci and abnormal values for plasma fibrinogen, albumin and globulin are generally absent, the serum calcium is normal or slightly subnormal, and the plasma cholesterol tends to be elevated. These chemical differences lend support to the theory that the two types of arthritis are quite different diseases.

Constitutional differences have long been suspected, it being frequently stated that atrophic arthritis tends to appear in tall, thin, viscerototic persons, hypertrophic arthritis in short, stocky, obese, sthenic individuals. According to Pribram²⁶¹ who determined the biotype of the two, the brachymorphic group rarely develops atrophic arthritis but has a decided tendency to develop hypertrophic arthritis. Thus of 24 patients with atrophic arthritis, 15 were eumorphic (normal body build), 9 dolichomorphic (tall, thin, shallow-chested, underweight), none was brachymorphic (short, thick, overweight). Of 26 patients with hypertrophic arthritis, 8 were eumorphic, 16 were brachymorphic and 2 dolichomorphic. However, there are frequent exceptions to these generalizations. Dawson¹⁰³ frequently noted atrophic arthritis in the short, obese, pyknic type and hypertrophic arthritis in the tall thin type (though perhaps not quite as early as in the former).

ATROPHIC ARTHRITIS

Incidence. Atrophic arthritis is presumably much less common in the tropics than in temperate zones. However, new reports indicate that it is fairly common in Egypt (Abdel-Sayed)²⁶². In Australia it is more common in the southern (temperate) regions (Cooper¹⁶¹) than in the northern (tropical) states, in the latter it is less common than rheumatic fever.

Symptoms and Course. Howitt²⁶³ stressed the importance of recognizing the "rheumatic diathesis," and the prodromes of atrophic arthritis: loss of appetite and weight, tachycardia, a fall in blood pressure, slight fever, sweating hands and feet, tremors, general nervousness, extreme fatigability—"symptoms referable to overstimulation of the katabolic group of endocrine glands." Although atrophic arthritis may begin at any time of the year, its greatest seasonal incidence in Dawson's¹⁰³ cases in New York City

was in the spring, especially March. In more than 80 per cent of his cases the onset was between the ages of 20 and 50 years, the greatest incidence being at 35, the earliest onset at 14 months and the latest, at 78 years. Three females were affected to one male. Although the onset of the disease is usually insidious, and occasionally subacute, it was acute in 8 per cent of his cases, at first resembling rheumatic fever. In 100 consecutive typical cases mitral stenosis was found in 7 per cent.

Subcutaneous nodules are present in about 20 per cent of cases¹⁰³. According to Neligan²⁶¹ there are two types of nodules in atrophic arthritis: "millet seed nodules," described by Coates and present also in "rheumatic children without cardiac lesions" and larger nodules, often painful, which may be an inch or more in diameter and may persist for years. Neligan saw a 59 year old woman with atrophic arthritis who had over 100 nodules in different sites, varying in size "from an inch across to that of half a split-pea." They were intermittently painful, pressure sores had formed over some.

Atrophic Arthritis and Splenomegaly, Relation to Still's Disease and to "Felty's Syndrome" Adenopathy is common in atrophic arthritis, occurring in from 40 (Douthwaite, 1933) to 53 per cent of cases (Coates and Delicati, 1931). An enlarged or palpable spleen is present in from 10 to 15 per cent (Dawson¹⁰³) to 21 per cent of cases (Coates and Delicati). Atrophic arthritis, adenopathy, and splenomegaly in adults have been called by some "adult Still's disease," but the majority regard Still's disease of children or of adults as a variety of atrophic arthritis. Moncrieff¹⁰⁴ did not accept this view and regarded Still's disease and juvenile atrophic arthritis as different diseases. He considered unproved the idea of certain continental physicians that Still's disease is of tuberculous origin.

Chauffard (1896) and Still (1897) described the syndrome of arthritis, adenopathy and splenomegaly. Hepatomegaly was not mentioned by either, anemia was emphasized by Chauffard but not by Still. In Still's cases joints were enlarged but no changes in bone or cartilage occurred even in advanced cases, hence the distinction from juvenile or adult atrophic arthritis. In 1909 Herringham noted the association of arthritis, splenomegaly and hepatomegaly in adults. In 1924 Felty reported cases of chronic arthritis, splenomegaly, anemia and leukopenia, and debated whether they were cases of adult Still's disease, arthritis coincident with Banti's disease, or of a distinct clinical entity.

Fitz²⁶⁵ continued the discussion on relationships and described a case of "Still's disease" and one of "Felty's syndrome." In the former case deforming arthritis and splenomegaly were present but no adenopathy. No description of roentgenograms was given to indicate whether or not intra-articular disease was absent, as described by Still. The patient with "Felty's syndrome" presented deforming arthritis, hepatomegaly, splenomegaly, anemia and leukopenia, and died suddenly of an undetermined cause.

Castellani^{-66, -67} distinguished between "Still's disease" and "febrile hepato-splenomegaly of adults with arthritis," describing 3 cases of the latter, of men aged 45, 54 and 61 years. Features of the disease were slow onset of malaise, arthritic pains, a somewhat undulating irregularly-intermittent or remittent fever, and great enlargement and firmness of the liver and spleen. One or several large or small joints were swollen and painful. Adenopathy was absent. The blood picture varied: slight leukocytosis, slight leukopenia or a normal blood count were present at different times in the same cases. Various agglutinins were absent. The disease was progressive. In one case death occurred in 14 months. Because "in Still's disease there is no true hepato-splenomegaly, the spleen being palpable but not much enlarged, and the liver usually of normal size" Castellani did not regard his cases as being ones of Still's disease.

(Obviously various physicians define Still's disease differently. As we stated before,² it is interesting to note variations in the response of the reticulo-endothelial system in cases of arthritis, but a new name for each combination seems unjustified. Dawson¹⁰¹ thought there was no merit in the clinical segregation of "Felty's syndrome" or in the use of the term itself, which should be discarded. Until other evidence is available we favor considering these "syndromes" as varieties of atrophic arthritis.—Ed.)

Pathology. Pathologic changes in three cases of atrophic arthritis were described by Parker and Keefer.⁻⁵⁶ Primary changes were synovitis, characterized by an increase in the number of synovial cells, with thickening of the membrane, destruction of some synovial cells, and collections of lymphocytes, macrophages, plasma and rare giant cells. In some regions these collections were perivascular (as described by Fisher, 1929), in others they were not perivascular (as described by Allison and Ghormley, 1931). In the fat of periarticular tissue were perivascular lymphocytic infiltrations, in periarticular muscle there was degeneration and atrophy. Secondary changes were destruction of cartilage, atrophy of bone due to disuse and not to active destruction, subluxation, fibrous or bony ankylosis and muscular atrophy. Additional changes were lymphoid hyperplasia, calcification of blood vessels, amyloidosis, disturbances of growth and pigmentation of skin. Parker and Keefer do not agree with Nichols and Richardson (1909) or Allison and Ghormley on the mechanism of cartilage destruction. The latter stated that as the synovial pannus passes over cartilage, it adheres and destroys the cartilage, which is simultaneously being invaded and destroyed by connective tissue proliferation from subchondral spaces. Parker and Keefer believed that cartilage destruction is not necessarily from subchondral invasion, but from a solution of cartilage under the connective tissue pannus and from a "dedifferentiation" of cartilage into connective tissue.

(Much can be learned from pathologic specimens, from whatever source obtained. However, it is unfortunate that clinical histories in two of Parker and Keefer's three cases were not available. The errors and inadequacies of Nichols and Richardson's

otherwise admirable report resulted from a paucity of clinical data. Pathologic reports of cases fully studied from the clinical, chemical and roentgenologic standpoint are highly desirable—Ed.)

Laboratory Data Blood Counts and Hemoglobin Anemia is commonly present in atrophic arthritis, but it is evidenced by a reduction in hemoglobin content rather than in erythrocyte count. In 92 cases Collins²⁶⁸ noted only a minor reduction of erythrocytes, but the value for hemoglobin was normal (14 gm or more) in only 18 per cent. The value for hemoglobin was 13 to 14 gm in 26 per cent, 12 to 13 gm in 30 per cent, 11 to 12 gm in 13 per cent, 10 to 11 gm in 11 per cent and less than 10 gm in 2 per cent. This simple hypochromic anemia was much more frequent in females and bore no constant relationship to gastric anacidity. Severe anemia was seen in patients with normal gastric acidity. Gray, Bernhard and Gowen²⁶⁹ found anemia much oftener among clinic than private patients owing to the poorer living conditions and more advanced arthritis of the former. Hemoglobin was less than 80 per cent in 50 per cent of their private patients and in 81 per cent of their clinic patients. Erythrocytes were below four million in 14 per cent of private patients, in 39 per cent of clinic patients. As the disease progressed the value for hemoglobin dropped. In early cases a leukocytosis (over 10,000) and a shift to the left were more frequent. Steinberg²⁷⁰ found the Schilling hemogram shifted to the left in 78 per cent of 42 cases of atrophic arthritis, but in only 17 per cent of 17 cases of hypertrophic arthritis. Correlated abnormalities in both blood counts and sedimentation rates were generally found, but when disagreement was noted, Steinberg considered an abnormal Schilling count of more value than the sedimentation rate in differentiating the two types of arthritis.

Sedimentation Rates The value of this test in the differentiation and prognosis is reaffirmed by several.^{27 34, 196 271 269} Gray²⁵¹ noted the following. In early atrophic arthritis, rates were 0 to 10 mm (per hour) in 23 per cent, 10 to 20 mm in 37 per cent, more than 20 mm in 40 per cent. In "established arthritis" they were 0 to 10 mm in 14 per cent, 10 to 20 mm in 25 per cent, more than 20 mm in 61 per cent. In "advanced arthritis" they were 0 to 10 mm in 8 per cent, 10 to 20 mm in 25 per cent, more than 20 mm in 87 per cent. Rates were more than 20 mm in only 2 per cent of cases of hypertrophic arthritis. The rate of sedimentation is believed to depend largely on the concentration of plasma fibrinogen and globulin and on cell volume.

Blood Proteins To determine reasons for altered sedimentation rates Davis²⁹ studied blood proteins. The total proteins of blood were normal in both atrophic and hypertrophic arthritis but, in atrophic arthritis, there was an increase in plasma fibrinogen and globulin, particularly the euglobulin fraction, and a fall in the albumin fraction. The albumin-globulin ratio was frequently below one, but tended to become normal as the patient recovered. Since rises in plasma globulin often occur in infectious diseases, Davis con-

sidered this evidence that atrophic arthritis is an infection. These alterations in proteins were not seen by Davis in hypertrophic arthritis. The findings of Aldred-Brown and Munio²⁷⁷ were essentially similar except that they found in hypertrophic arthritis also a reduction of serum albumin, though not nearly so much as in atrophic arthritis.

Cholesterol The total plasma cholesterol tends to be decreased in atrophic arthritis (increased in hypertrophic arthritis, Hartung and Bruger²⁵⁹). The mean total cholesterol in 33 cases was 175.2 ± 39.5 mg per 100 c.c. of plasma. The cholesterol was normal (160 to 230 mg) in 49 per cent, below normal in 39 per cent and above normal in 12 per cent. The cholesterol partition (free ester) was normal. No correlation existed between sedimentation rates and cholesterol. Hypocholesteremia tends to support the infectious theory since other acute infections are accompanied by it.

Serum Calcium and Phosphorus Normal values were found in the 200 cases of Lahey and Haggart²⁷¹ and in all but one seen by Gray, Bernhard and Gowen²⁶⁹, one case had a low calcium-phosphorus index. Hartung and Greene²⁷⁸ found the values for the mean and standard deviation in 50 cases to be 10.218 ± 0.699 mg. calcium per 100 c.c., the same as in control cases. The serum calcium was slightly lower in hypertrophic arthritis. These findings do not quite agree with those of Race²⁶⁰ who noted a small but definite tendency to lower values in atrophic than in hypertrophic arthritis.

Magnesium Serum magnesium was essentially normal in both types of arthritis (Race²⁶⁰). Values were slightly lower in atrophic than in hypertrophic arthritis.

Blood Groups In 1000 cases of rheumatism (atrophic and hypertrophic arthritis, "subacute rheumatism," fibrositis) Race²⁶⁰ found the blood groups that would be expected from a random sampling of the general population.

Blood Pigments In cases of atrophic arthritis with a rapid sedimentation rate Race²⁶⁰ often found a marked diminution of plasma pigments. The icteric index was often as low as 3 units, sometimes even lower (normal about 6 units). Studies were in progress to determine whether the low plasma color was due to reduced lipochromes, bilirubin or both.

(These observations are of interest in connection with those of Hench (1933-34)⁴⁹ and of Sidel and Abrams (1934) that jaundice may induce a rapid and prolonged remission in cases of atrophic arthritis and of fibrositis—Ed.)

Urine Ellis (1927) and others suggested that there was an "alkaline diathesis" (deficient acid elimination) in atrophic arthritis, an "acid diathesis" (deficient alkali elimination) in hypertrophic arthritis. Race²⁶⁰ was unable to substantiate this contention. Urinary calcium was normal, and the pH, acidity, formol acidity and phosphate excretion were equal in both types.

Gastric Analysis Among 53 patients with atrophic arthritis Collins²⁸⁸ noted achlorhydria in 23, hypochlorhydria in five, normal acidity in 23 and

hyperchlorhydria in two. Reduction of acids bore no constant relation to anemia present. Hartung and Steinbrocker²⁷² noted achlorhydria in 27 per cent, hypochlorhydria in 17 per cent of 35 cases of atrophic arthritis, and achlorhydria in 26 per cent, hypochlorhydria in 3 per cent of 35 cases of hypertrophic arthritis. They considered that an abnormal frequency in the occurrence of subacidity is an important feature of chronic arthritis.

Electrocardiograms. The electrocardiograms in 50 cases of acute atrophic arthritis were found to be essentially normal by Master and Jaffe,¹⁹¹ in sharp contrast to those in cases of acute rheumatic fever.

Synovial Fluid. Normal synovial fluid probably contains about 200 cells per cu mm of which less than 10 per cent are polymorphonuclear cells, according to Collins.²⁷³ The total nucleated cell counts in 35 cases of atrophic arthritis were high (5,000 to 60,000 cells per cu mm). Counts in most cases were 10,000 to 20,000 cells. The percentage of polymorphonuclear cells varied from 40 to 90 per cent, in the great majority of cases being 70 to 90 per cent. These data agree essentially with those of Kcefer, Myers and Holmes (1934). The consistently elevated protein content of synovial fluid indicated the presence of an exudate, not a transudate. The ratio between blood and synovial sugar content was never significantly altered in atrophic arthritis. (In bacterially-infected fluids in specific infectious arthritis synovial sugar is usually markedly reduced—Ed.)

Etiology and Pathogenesis. The literature of 1935 repeated familiar arguments on etiology. Factors previously considered are again regarded as causal: the factor of infection, of trauma, of circulatory disturbance, of altered metabolism, of endocrine abnormality, and of neurogenic disturbances. Each factor is regarded by some as the essential one, the other factors being contributory.

Factor of Infection. Evidence for the theory of infection is direct and indirect. Direct evidence is presumably derived from cultures of blood, infected foci, lymph nodes, joint tissues and fluid, and from studies on the tropism and cataphoretic velocity of bacteria isolated therefrom.

1. *Blood cultures.* Gray^{251, 269} and his colleagues reported isolation of streptococci, mostly alpha (viridans) or alpha prime, from the blood in 48 per cent of 200 cases. Cases of early arthritis gave a much higher (65) percentage of positive cultures than those of established arthritis (positive in 36 per cent) or of advanced arthritis (positive in 26 per cent). Few positive blood cultures were obtained in summer. Cultures from infected foci often yielded the same types of streptococci. A small percentage of blood cultures yielded staphylococci and diphtheroids of undetermined significance. Control blood cultures were negative in all of 36 "normal" persons, and in all of 79 cases of hypertrophic arthritis, they were positive in 23 per cent of 22 cases of "acute focal infection," in 4 per cent of 26 cases of "chronic focal infection," and in 8 per cent of 89 cases of "arthralgia." (Were the latter cases of periarticular fibrositis?—Ed.)

Streptococci, generally "viridans," occasionally "hemolytic," were found

in 21 per cent of patients with atrophic arthritis, in 6 per cent of controls, by McEwen, Bunim and Alexander²⁹

2 *Other cultures* Although a variety of methods was used, cultures of synovial fluid were all negative in Collins' cases²⁷ Key³⁰ was unable to isolate streptococci from articular tissues, but found staphylococci in a third of joints studied. Streptococci of the alpha (viridans) or gamma (non-hemolytic) type were found by Gray and his colleagues^{31, 32} in 30 per cent of stools examined

3 *Electrophoretic velocity* Rosenow³³ again noted that streptococci, isolated in cases of atrophic arthritis and having a marked affinity for joints of animals following intracerebral injection, had a markedly "arthrotropic" cataphoretic velocity, usually 2.3 microns per second, volts per centimeter. Streptococci similarly isolated in cases of encephalitis had little or no affinity for joints but marked affinity for brains of animals and a markedly "neurotropic" cataphoretic velocity, usually 3.45 or 1.72 microns per second, volts per centimeter. The velocity of streptococci isolated from patients with "neuromyositis" was distributed between neurotropic and arthrotropic, about half of them having a neurotropic, the other half an arthrotropic potential. Previous similar work by Rosenow and Jensen (1930) was confirmed by Wood, Jensen and Post³⁴ who studied the cataphoretic velocity of streptococci (generally viridans, occasionally hemolytic rarely the "indifferent" type) isolated from 1173 cultures from foci in 215 cases of "focal infection diseases" including 90 cases of atrophic arthritis and 70 of neuritis. The method of cataphoresis was found useful in detecting reactions between antibodies and homologous bacteria. Given a stock suspension of bacteria with known pathogenicity and known mobility, specific antibodies in a patient's serum could be detected.

When Pratt, Sheard and Rosenow exposed them to short-wave radiation, arthrotropic streptococci lost their characteristic arthrotropic electrical potential and their affinity for joint tissues, and assumed the velocity of neurotropic bacteria and an affinity for brain. Conversely, neurotropic streptococci became arthrotropic and acquired affinity for joints. Changes thus induced were maintained in subcultures of these organisms^{27b, 27c}

(These experiments were done on bacteria in vitro. Do they suggest that exposure of an arthritic patient with arthrotropic streptococci to short wave therapy might change the invasive character of the patient's bacteria and his symptoms and make him "neuritic"? Rosenow's clinical colleagues treated a few arthritic patients with short wave therapy. Such clinical mutations, perhaps theoretically possible, have not been noted by them, or reported by others using short wave therapy.—Ed.)

4 *Indirect evidence* Indirect evidence supporting the infectious theory is derived from skin reactions to injections of certain bacteria, from the presence of agglutinins, precipitins, antifibrinolysins, and antistreptolysins, and from complement-fixation reactions

a *Skin tests* "Positive skin reactions" to one or more strains of

streptococci were found by Wainwright²⁷⁸ in 75 of 78 cases. A maximal reaction was to hemolytic streptococci in 88 per cent, to green streptococci in 8 per cent. Three cases showed no reactions. Skin reactions were absent in two and present in one case of Still's disease, absent in four and present in six cases of hypertrophic arthritis. Reactions diminished or disappeared when patients were treated with vaccines made from streptococci to which their skin was sensitive. Keefer²⁷⁹ and Dawson¹⁰³ have reminded us of the wide divergence in results obtained with such tests, and that their interpretation is difficult. All arthritic patients do not show positive reactions, some may react to organisms not found in their foci. In a given case a "positive skin test" does not in any way prove a causal relationship between the bacteria used and the patient's disease, although it may suggest that the patient is either infected with or is a carrier of the bacteria in question.

b Agglutinins Agglutinins to hemolytic streptococci, generally in high titer, were found in serums by Wainwright²⁷⁸ in 90 per cent of 87 cases, by McEwen, Bunim and Alexander²⁸⁰ in 88 per cent of 37 cases, by Blair and Hallman²⁰⁶ in 85 per cent of 62 cases. According to Dawson¹⁰³ significant agglutination occurs only with hemolytic streptococci, group A (Lancefield). Agglutinins for this group were usually definitely present in the cases of McEwen, Chasis, and Alexander²⁸⁰ but definite reactions were also obtained with other hemolytic streptococcal groups. Of Gray's²⁵¹ cases, 70 to 76 per cent had agglutinins (presumably to green streptococci, "alpha or alpha prime") in dilutions from 160 to 5120. Blair and Hallman²⁰⁶ found no correlation between agglutinin titers and the patient's age, duration of arthritis, number of joints involved or sedimentation rate. Others²⁰⁹ found it difficult to understand why titers increased in some and decreased in others who were progressing satisfactorily, and why titers increased one month and decreased the next. During the treatment of Wainwright's patients with streptococcal vaccine the agglutinins materially increased²⁷⁸.

The presence of such agglutinins is regarded by many^{103, 278, 279} as the strongest evidence in favor of the infectious theory of atrophic arthritis. They are found only rarely in patients with hypertrophic arthritis or in normal persons^{103, 206, 278}. Because, however, hemolytic streptococci can be isolated so rarely from affected joints, and because antifibrinolysins are *not* increased in atrophic arthritis (as they are in proved hemolytic streptococcal diseases and in rheumatic fever) one cannot finally conclude that the presence of streptococcal agglutinins indicates a causal relationship (Wainwright²⁷⁸). Keefer²⁷⁹ raised the question: Are these reactions a direct response to streptococcal infections, or are they indirect responses of a non-specific nature such as one sees in syphilis and typhus fever?

Formerly Rawls and Chapman²⁸¹ treated patients with vaccines made only from strains which patients' serums agglutinated, and inagglutinable strains were discarded as of no etiologic significance. Because some patients

so treated did not receive benefit, it was surmised that agglutination tests might not be reliable criteria for determining pathogenic specificity, since some causal strains might be inagglutinable (Freshly isolated strains of typhoid bacilli are sometimes inagglutinable—Ed.) Seeking more reliable tests of specificity, Rawls and Chapman²⁸¹ determined not only the agglutination tests, but the ability of strains of streptococci (isolated from infected foci of arthritic patients) to resist the "bactericidal" action of freshly-diluted defibrinated guinea-pig's blood in conjunction with their ability to produce arthritis in rabbits. Agglutinable strains killed by guinea-pig's blood produced arthritis in 88 per cent of injected rabbits, although large doses and multiple injections were required. Non-agglutinable strains killed by guinea-pig's blood produced arthritis in only 30 per cent of injected rabbits. Agglutinable strains not killed by guinea-pig's blood produced arthritis in 92 per cent of injected rabbits. The most pathogenic, however, were non-agglutinable strains not killed by guinea-pig's blood—these produced arthritis in 100 per cent of injected animals. Rawls and Chapman therefore concluded that certain inagglutinable strains were more pathogenic than agglutinable strains, particularly if they were also resistant to the bactericidal effect of guinea-pig's blood, and that agglutination tests in conjunction with tests of the resistance of a strain to the bactericidal action of guinea-pig's blood are of more value in assaying the specific pathogenic potentialities of any particular streptococcus than agglutination tests alone.

c Precipitins Precipitins for the C substance of hemolytic streptococci were found by McEwen and his colleagues²⁸⁰ in the blood of 80 per cent of 37 patients with atrophic arthritis, but they were also frequently found in other types of arthritis, even gonorrheal. In appraising their significance, therefore, caution must be exercised. There is a close approximation but not an absolute agreement between agglutination and precipitin reactions (Dawson¹⁰³).

d Antistreptolysins Antistreptolysins were increased (over 100 units per c.c.) in the blood of only a few of McEwen's²⁹ patients, and in the blood of only a third of Blair and Hallman's 45 patients²⁰⁶. In the latter cases high antistreptolysin titers with one exception accompanied high agglutinin titers. Of 32 miscellaneous serums tested for antistreptolysin, only seven gave high titers, two from cases of atrophic spondylitis, five from cases of chronic osteomyelitis.

e Antifibrinolysins Antifibrinolysins were not found by Myers, Keefer and Holmes²⁰⁸ in plasma in 11 cases and were only occasionally found by McEwen²⁹. Since antistreptolysins and antifibrinolysins are indexes of recent, acute, hemolytic streptococcal infection, perhaps one should not expect to find them in cases of chronic atrophic arthritis, although they are sometimes found in early acute cases.

f Complement-fixation tests These tests with streptococci were usually negative in cases of "acute or chronic polyarthritis" seen by Beck and

Coste⁻⁰⁷ They were usually positive to several streptococci, staphylococci and colon bacilli in the few cases of Gray et al⁻⁰⁹ who regarded the test subject to considerable error unless rigidly controlled. An occasional patient with atrophic arthritis gave an unexplained positive complement-fixation test to gonococci.

5 *Interpretation of evidence for the theory of infection* Investigators are discouraged in their attempts to discover direct indisputable evidence for this theory, hence their activity in searching for strong indirect evidence from various serologic and other reactions noted. An interpretation of these reactions is not now possible. Most of them are only relatively specific for atrophic arthritis, they are generally not specific for one bacterial strain and at best suggest, but do not prove, a causal association with streptococci. Indirect or circumstantial evidence is never as satisfying or convincing as direct evidence, nevertheless one cannot disregard it. One cannot deny the value of indirect evidence if it is found to be practically "specific." In the diagnosis of syphilis we have learned to rely heavily on the indirect evidence of an accurate serologic reaction, we no longer hunt for direct evidence—the *Spirochaeta pallida*. This analogy is worthy of further comment. The value of a positive Wassermann reaction lies in the fact that it is only "specific" to the extent that it is essentially pathognomonic of syphilis for the actual presence of spirochetes is not necessary for the reaction. Some by-product of the disease is responsible for the reaction. Hence it is possible that various streptococcal immune bodies in atrophic arthritis (and rheumatic fever) are by-products of the disease, responsible for reactions which may be proved to be more or less "specific" or pathognomonic of atrophic arthritis even though streptococci may not actually be the specific cause of the disease. Evidence for the theory of infection continues to be highly suggestive but is not yet conclusive.

The Theory of Bacterial Allergy Hypersensitiveness, not to one, but to several bacterial strains, proposed as a way out of this dilemma, is accepted by some,²⁸² but is meeting with increasing objections from others. Freeman's²²⁰ criticism of the theory was noted under the discussion on rheumatic fever. Keefer²⁷⁹ also regarded it as unproved. Although in many ways the hypothesis sounds attractive, Dawson¹⁰¹ concluded that "it is supported by singularly little evidence."

Virus Theory Coles²²² found "numerous virus bodies" in the synovial fluid in five of nine cases of atrophic arthritis. He regarded them of the same species as those he found in cases of rheumatic fever. No animal studies were made, hence no conclusions could be drawn.

Factor of Trauma That acute or chronic trauma from occupation, poor posture or recreation can predispose to, precipitate or aggravate atrophic arthritis is again emphasized by Hall¹³ and by Archer²⁸³. The latter believed that repeated trauma may produce atrophic as well as hypertrophic arthritis.

Factor of Circulatory Disturbance No new definite evidence is presented. Björkman²¹¹ regarded the local and systemic manifestations of atrophic or hypertrophic arthritis (as well as of fibrositis) as caused by local exudation from "cold edema."

(No proof is offered—Ed.)

Keefe²¹⁰ and Dawson¹⁰¹ cannot accept the idea that atrophic arthritis is caused by circulatory disturbances, because arthritis is not a complication of occlusive vascular disease and is infrequently associated with Raynaud's disease or scleroderma, because delayed removal of sugar from the blood of arthritic patients is variably present and also present in certain non-arthritics, and particularly because synovial membrane in atrophic arthritis reveals, not a decreased, but rather an increased blood supply, with many wide open capillaries.

(These pathologic findings link up with the bone atrophy present, for Jones and Roberts, 1934, found that bone becomes partly decalcified when its blood supply is increased, but becomes hypercalcified if its blood supply is decreased—Ed.)

Factor of Altered Metabolism Current theories are that there is a disturbance of sulphur metabolism, of liver function, or a vitamin deficiency, a food allergy, or an intestinal toxicosis. The origin of the idea that arthritis may result from abnormal sulphur metabolism has been reviewed by several^{215, 281-287}. The cystine content of certain tissues, such as finger nails, is considered a reliable guide to the sulphur metabolism of the body. The normal cystine content of nails ranges from 10.4 to 13 (average about 11.8) mg per 100 cc (Wheeldon,²¹⁵ Rawls, Gruskin and Ressa,²⁸¹ Argy,²⁸⁸ Sullivan and Hess, 1934). In "arthritic patients" the range is 6.5 to 13 mg (average variously reported at 8.2 to 9.8) (Sullivan and Hess, 1934, Argy,²⁸⁸ Woldenberg²⁸⁷). The range in Woldenberg's patients was 6.5 to 9.8 mg before, and 11.6 to 13 mg after, sulphur therapy. The cystine content of nails and the sedimentation rate of erythrocytes varied in inverse proportion²⁸⁸. Hess²⁸⁹ noted these concentrations in normal nails: cystine by the Sullivan method, 11.98 mg per 100 cc, and by the method of Vickey and Block, only 9.57 mg; arginine 6.6 per cent, histidine 0.46 per cent, and lysine 2.61 per cent. In the nails of patients with "arthritis" Hess found cystine, 9.78 per cent (Sullivan method), arginine, 6.62 per cent, histidine, 0.49 per cent, lysine, 2.63 per cent. Thus in nails of arthritics the three basic amino-acids were essentially normal, but the cystine was reduced. These workers made no attempt to subdivide "chronic arthritis." In atrophic arthritis Wheeldon²¹⁵ found the cystine content of nails was 7.9 to 10.6 (average 9.65) mg, after sulphur therapy the average rise was 1.63 mg. (In hypertrophic arthritis the content was 8.2 to 10.6, average 9.27 mg, after sulphur therapy the average rise was 2.35 mg.)

Because of these findings Wheeldon²¹⁵ suggested that "at least some, if not all, forms of arthritis are made possible by a sulphur deficiency, par-

ticularly in the cartilage of the joints, that, given a sufficient sulphur reserve to combat the contributing etiologic factor arthritis would not occur, and that, whether there is a sufficient sulphur reserve or not depends upon the ability of the intestinal tract normally to absorb sulphur."

Race⁶⁰ does not interpret the findings thus. The lowered cystine content of nails may be due, not to a disturbance of general sulphur metabolism, but to the reduced albumin-globulin ratio in blood plasma. The cystine content of globulin is lower than that of albumin, and the amount in nails may merely reflect alterations in plasma proteins. In a few cases of atrophic arthritis Race found a reduced blood glutathione, which probably resulted from the reduced number of erythrocytes as there is little or no glutathione in plasma. (Other evidence has been presented in favor of an abnormal sulphur metabolism. Goldthwaite (1904) noted loss of sulphur in atrophic, and sulphur retention in hypertrophic arthritis. Cawadinas (1925) reported a negative sulphur balance, indicating increased sulphur catabolism in "chronic rheumatics." Race (1927) denied the existence of a negative balance but noted increased urinary excretions of neutral sulphur in 20 of 42 patients with atrophic arthritis—Ed.) Senturia²⁵⁷ studied the sulphur excretion and partition in the daily urine of 18 patients with atrophic and 41 with hypertrophic arthritis. No appreciable deviations from those in 20 healthy persons were noted. His experiments tend to disprove the alleged existence of abnormal sulphur elimination or sulphur partition in the urine of arthritics.

Hepatic Dysfunction This is regarded by Todd²⁹⁰ as one of the basal factors in "chronic rheumatism." He noted the transient appearance of chronic muscular or articular rheumatism subsequent to catarrhal jaundice in certain cases. Tests for hepatic dysfunction were frequently more "positive" during periodic bouts of rheumatism than in subsequent remissions. (No details and no evidence thereof were given—Ed.)

Using the levulose tolerance test and considering a rise of 30 mg or more above the initial level in the blood during the test as evidence of hepatic inefficiency, Miller⁶¹ found some degree of hepatic impairment in about a third of all his rheumatic patients, in 31 per cent of 117 cases of atrophic arthritis, in 37 per cent of 41 cases of hypertrophic arthritis, in 36 per cent of 68 cases of fibrositis, in 28 per cent of 18 cases of sciatica, and in 33 per cent of 6 cases of gouty arthritis.

(He noted that Kimball (1932) found an abnormal levulose tolerance test in only one of 10 cases of chronic arthritis—Ed.)

Vitamin C Deficiency Subacute or chronic vitamin C deficiency produces in guinea-pigs an arthropathy which Rinehart²³³ believed was markedly similar to atrophic arthritis. Synovial proliferation, pannus formation, periarticular thickening, bone overgrowth and subcutaneous nodules are produced. Superimposed infection may accentuate the pathologic process. Rinehart was unable to produce arthritis with infection in the presence of adequate vitamin C nutrition. However, when vitamin C deficiency was first produced, areas of diminished resistance to subsequent infection re-

sulted. Infection plus vitamin C deficiency more readily produced scorbutic arthropathy in animals, lesions of which resembled those of atrophic arthritis. Many of the prodromal symptoms of atrophic arthritis are characteristic of latent scurvy. Some of his patients with atrophic arthritis presented evidence of vitamin C deficiency. Rimelhart therefore suggested that vitamin C deficiency may be a factor in the etiology of some cases called "atrophic arthritis."

Dietary Habits No direct relationship between dietary habits and chronic arthritis could be found by Hall and Myers,²⁹² who studied the dietary habits of 40 patients with atrophic and 27 with hypertrophic arthritis and 30 controls. No striking single abnormality in diet of any one group was found. Inadequate calories were consumed by 20 per cent of those with atrophic arthritis, by 37 per cent of controls. (Excess calories were taken by 59 per cent of those with hypertrophic arthritis, by 43 per cent of controls.) "Undesirable diets" were taken by 50 per cent of those with atrophic arthritis, by a third of those with hypertrophic arthritis, and by 40 per cent of controls. Some but not all arthritic patients took carbohydrates to excess and got inadequate vitamins and minerals, but so did some of those without arthritis.

Intestinal Toxicosis This condition causing arthritis may result according to Gutman²⁹³ from the improper metabolism of food as well as from infection in the "pathologic colon." However, Keefer²⁷⁹ found no constant deviation from normal gastrointestinal function in arthritis. Gastric anacidity, carbohydrate indigestion, and "abnormalities" in the colon are found inconsistently and no oftener than in other diseases, and there is no proof that they are significantly related to the course of the arthritis. Keefer found no gross or histologic evidence of atrophy or other disturbance in the intestines of four patients who died with atrophic arthritis.

Food Allergy Many persons are hypersensitive to certain foods and develop acute symptoms of various sorts. Some of these patients have a coincident atrophic arthritis. It has been suggested that the arthritis is related primarily or secondarily to the food allergy (Brown, G. I.²¹⁴), that the arthritis may be an allergic reaction to offending foods, or that an atrophic arthritis can be made worse by subsequent attacks of food hypersensitivity. No convincing evidence has ever been offered, new data are inconclusive. Among many patients Bauer²⁹¹ never saw one whose atrophic arthritis was traceable to food hypersensitivity.

Factor of Endocrine Abnormality Many physicians speak vaguely of endocrine abnormalities associated with or responsible for arthritis, but specific data are rarely given and definite evidence that such abnormalities occur in a significantly greater percentage of arthritics than in normals or persons with other chronic diseases is not at hand. Howitt,²⁹³ for example, considered the prodromal symptoms of atrophic arthritis "referable to

overstimulation of the katabolic group of endocrine glands, for atrophic arthritis is, like exophthalmic goiter and diabetes, a disease of the endocrine-sympathetic system" Todd²⁹⁰ stated that in chronic rheumatism, "subthyroidism is frequent. A pituitary factor is not infrequent. Ovarian dysfunction with oligomenorrhea or amenorrhea is common in atrophic arthritis." Another²⁹¹ contributed this gem: "Experience points to a close connection between arthropathies and endocrine glands. Constitutionally the dolichomorphic type, probably governed by the anterior pituitary, thymus and interstitial gonads and influenced by the thyroid and adrenal glands is associated with atrophic arthritis, while the brachymorphic constitution, dominated apparently by thyroid, Langehansian body and gonads, seems most frequently connected with the hypertrophic type" (There we are, its as clear as that! But to make it easier certain endocrines were recommended "whenever the condition demands opotherapy"—Ed.)

1 Alterations in thyroid function. Some consider hypothyroidism, others hyperthyroidism, causally related to arthritis and report significant deviations from the normal metabolic rate fairly frequently in arthritics. Hall and Monroe (1933) found rates below — 10 in 36 per cent of cases, and below — 17 in 18 per cent. However, Monroe²⁹⁰ reported that the incidence of atrophic arthritis in 98 cases of myxedema and in 414 cases of hyperthyroidism was low, probably no more than would be expected statistically. Of the hyperthyroid patients, 3 per cent had atrophic arthritis, 2 per cent had hypertrophic arthritis, 4 per cent had arthralgia or myalgia, 1 per cent had bursitis, and 90 per cent had no joint disease. Of the myxedematous patients, 3 per cent had atrophic arthritis, 5 per cent had arthralgia and myalgia, none had bursitis, 60 per cent had no rheumatism, but 33 per cent had hypertrophic arthritis. This may have been due to the fact that the average age (51 years) of the myxedematous patients was 15 years greater than that of the hyperthyroid group, an age when hypertrophic arthritis makes its almost universal appearance.

Duncan (1932) stated that patients with preexistent atrophic arthritis showed exacerbations of symptoms when hyperthyroidism developed, that joint pains were often associated with hyperthyroidism, and that thyroidectomy afforded marked, prompt relief to joints. Bach²⁹⁷ reported three such cases. One case was detailed that of a young woman with polyarthritis and "slight but definite signs of hyperthyroidism" which later became marked. After thyroidectomy "immediately the pains, stiffness and periarticular swelling disappeared" without recurrence.

(It is the belief of the majority of the editors that the relief experienced in some cases from thyroidectomy, parathyroidectomy and so forth is quite nonspecific, the result not of *the* operation, but of *an* operation, and that almost any surgical operation may produce similar results. Such dramatic relief is often seen in the upper extremities after lumbar sympathectomy, it is also seen after appendectomy, cholecystectomy, tonsillectomy, and splenectomy. Unfortunately the relief is usually transient, merely a brief remission having been induced. Occasionally, however,

relief is prolonged. In evaluating the effect of any surgical procedure in arthritis one must [but most writers do not] take this nonspecific postoperative effect into account. However, one of us, A. A. F., believes that the correction of hyperthyroidism may exert some "specific" influence on the course of the disease—Ed.)

Metabolic rates were determined by Gray, Bernhard, and Gowen²⁶⁹ in 47 cases of atrophic arthritis, 53 per cent gave minus readings (average -7), 47 per cent gave plus readings (average $+14$). The rate tended to drop as the disease progressed, the average rate in cases of advanced arthritis was -9 . In two cases hyperthyroidism developed, the effect of thyroidectomy thereon was not noted.

(These figures do not tell us much. It is not stated how many cases had definitely abnormal rates—over 15 or under 15 per cent—Ed.)

Race²⁶⁰ and Dawson¹⁰³ concluded that patients with atrophic arthritis show no significant deviation from rates seen in a group of normal or chronically ill persons.

2. Parathyroid dysfunction has recently been advanced as the cause of certain cases of arthritis, including the atrophic type, and particularly of ankylosing spondylitis. Parathyroidectomy is being performed²⁶⁸. The subject will be discussed later under "Relationship between arthritis and hyperparathyroidism". Suffice it to say here that Lahey and Haggart²⁷¹ found in 200 cases of atrophic arthritis no clinical, chemical or roentgenographic evidence of hyperparathyroidism.

Factor of disturbance of the sympathetic nervous system. Although several of the year's writers glibly spoke of atrophic arthritis resulting from disturbances of the sympathetic nervous system, no new data to support the idea are at hand. Disturbances of the sympathetic system have been considered responsible for the vasomotor symptoms of the disease. These symptoms can be largely cured by sympathectomy, but opinions differ as to whether the arthritis is also cured thereby. Keefer²⁷⁰ stated that before one can blame arthritis on these vasomotor symptoms it must be shown that (1) all patients have these changes prior to their arthritis, (2) vasomotor reactions are capable of producing inflammatory changes in synovia, (3) the arthritis can be arrested by sympathectomy. It was his opinion that vasomotor disturbances undoubtedly contribute to the symptomatology of atrophic arthritis, but that neither they nor other functional alterations in the sympathetic nervous system have been proved responsible for the disease, or their sole correction entirely responsible for a cure.

Relation of Atrophic Arthritis to Rheumatic Fever. This was discussed under the section on rheumatic fever.

Relation of Atrophic Arthritis to Tuberculosis. Some believe that many, if not all, cases of atrophic arthritis represent "tuberculous rheumatism," an atypical, possibly allergic, reaction induced by tubercle bacilli (Copeman¹⁰⁰). The idea was discussed under "Tuberculous rheumatism". Forestier⁴¹ spoke of an attenuated form of tuberculous arthritis of the

fibrous type, a transition type between true atrophic arthritis and what the French call "tumeur blanche". Tuberculosis was rare among Dawson's¹⁰⁷ 800 patients with atrophic arthritis, only three having it. Moncrieff¹⁰¹ accepted the evidence that positive tuberculin reactions in arthritic children are no more numerous than one would find in a group of healthy children of the same ages.

Conclusion on Etiology No extended comment is necessary. Obviously the cause of atrophic arthritis is unknown. At present the infectious theory remains dominant (and we feel rightly so), but it is far from proved.

Treatment—General Remarks Arthritis is one of the two diseases most poorly treated by physicians, according to Yater²⁹⁹ who, however, found excuses therefor. Chronic arthritis requires months or years of consistent treatment, which is difficult when most patients change physicians so often. Markedly disabled, the patient may be unable to earn money for proper treatment. Little is known regarding the cause or cure of the disease, and, as to what is the best treatment, there is much confusion in the minds of general practitioners. (In the minds of some "rheumatism specialists" also, may we add—Ed.)

Those of wide experience agree that since no "specific" for the disease is at hand, the patient and not just his disease must be treated, perhaps the patient even more than the disease. A broad approach to the problem of treatment is required, and regardless of individual opinions on the relative importance of this or that causal factor, whatever physiologic abnormality a patient presents, whatever coincident or related infection, endocrine or metabolic disturbance, or postural or occupational strain, is present should be corrected as far as possible in order to help the patient cure himself of a disease which the physician can't, or hasn't yet learned how to, cure.

This necessitates a "combined attack," but the attack is intended to overwhelm the disease, not the patient, and the latter must not be swamped by a too energetic or too inclusive treatment. The plan of treatment must therefore be individualized to suit the requirements of each patient at the moment. The program of therapy should have latitude and longitude. First will be used, not every accepted form of treatment, but only a selection of those measures which the stage of the disease, and the patient's physiologic make-up, constitution, and finances, warrant. In the first few weeks of a rather healthy patient's mild disease one perhaps could not well defend treatment by radical removal of foci to the extent of removing, for example, a questionably-infected gall-bladder or a hyperemic cervix. A little later, however (but not too late), when the arthritis appears formidable such measures may be defensible.

In the presence of a poor patient with an obviously subsiding chronic arthritis one could hardly defend the institution of a long and expensive course of even the most touted vaccine. In some regards nature is a poor rheumatism specialist, particularly when she fosters flexion deformities and ankyloses. But nature may be a good physician if given a chance and

helped, not hindered, especially early in the disease, when the patient is so apt to traumatize his diseased joints and to deplete his strength by sleepless nights and anxious days. When it is apparent that a benign nature has things under control, it is perhaps best for the physician to be an admiring spectator and not a too obtrusive fellow-actor. If physiologic equilibrium is being satisfactorily obtained without vaccines, it is best to hold their use in abeyance, since we know too little about the mechanisms involved and may do harm, not good. If, however, one is faced with a relentlessly progressive disease, it seems folly to withhold vaccines "because they only help one in three or four." That fourth patient deserves his chance for relief. At times, therefore, the combined use of several measures may be necessary, and the program may quite justifiably include certain fairly safe remedies which are not yet "standard."

The program of treatment must also have longitude. It must be planned so that it can be kept up over a long period of time as efficiently, and yet as inexpensively, as possible. This means substitution of at least part of professional physiotherapy by home physiotherapy, the use of the less expensive (but just as good) analgesics by mouth rather than fancy-named salicylates or other medicines by vein. The physician must foresee the probable necessity of modifying treatments to meet changing circumstances. He should be planning what to do next if in a particular case the current program fails after a reasonably, but not unreasonably, long trial period. The patient should know that the physician does have a second, third or even fourth line of defense, that other measures with a reasonable likelihood of success are available as necessary. This creates the confidence and optimism so vital to the arthritic patient. Although the physician may alter details of treatment from time to time, he will constantly impress upon the patient the importance of continuing those fundamental principles of treatment which apply to all chronic, especially infectious, diseases—the necessity of extra periods of rest, adequate diet and so on.

The array of measures suggested hereafter shows only too well that no one remedy is consistently helpful. Each must be regarded as part of a mosaic, not to be used alone or judged too much on its own merits. Herein, however, lies the difficulty in evaluating researches on treatment, for in most cases the measure used was but part of a larger plan of treatment, though the writer often fails to mention the fact. *Thus the matter of setting up controls is so difficult, yet so important.*

Infected Foci and Their Management The controversy as to relationship between infected foci and chronic arthritis is still actively discussed^{279, 282-300}. Pemberton²⁵³ again stated that many infected foci are the result, not the cause, of the disease. Of 300 patients with "chronic arthritis," 66 per cent of those with atrophic and 47 per cent of those with hypertrophic arthritis had had infected foci removed before he saw them. Nevertheless he found infected foci in 79 per cent of those with atrophic and in 81 per cent of those with hypertrophic arthritis. Obviously the pre-

vious removal of infected foci had either been done incompletely, or other foci had subsequently developed. Obviously, also, many were not helped by removal of such foci. However, others believe that results obtained from the removal of foci leave little doubt as to the value of this procedure, which in their opinion is the *sine qua non* of therapy^{300, 301}. Removal of foci alone is rarely successful, and when it is to be done in the case of depleted malnourished patients, the patient should be "built-up" beforehand³⁰². One should distinguish according to Sherwood³⁰³ between unwall-off infected foci which may produce systemic disease, and walled-off infections such as dental-root cysts, which he considers harmless.

If removal of a focus is followed by either exacerbation or disappearance of the arthritis, a relation between focus and joints is generally assumed. However, improvement following removal of foci may be due to a general "stimulation resulting from removal of one cause of a lowered resistance"^{279, 282}. When neither improvement nor exacerbation occurs it is assumed that the removed focus was not the cause, or that the arthritis was too established for focal removal to help. Stated reasons for doubting the theory of focal infection include failure of improvement in arthritis after removal of foci, cases of arthritis without demonstrable foci, improvement of arthritis without removal of foci, frequency of infected foci in non-arthritics, and inability to obtain consistently the same bacteria from foci and joints.

1 Teeth. Some favor the removal of dead teeth,²⁸² others consider them harmless and remove only definitely infected teeth^{34, 103, 300}. If many are to be removed, some remove four or five at a time, with intervals of two weeks between sessions.

2 Tonsils. Of 500 patients with "arthritis" seen by Nissen,³⁰⁴ 10 per cent had had their tonsils removed prior to the onset of the disease. 90 per cent had not. The course of the arthritis in these two groups was studied. Infected tonsils should be removed only during a period of relative arthritic quiescence. If such a period does not appear, or if in a given case the arthritis is constantly progressive, Nissen believed "tonsillectomy is never indicated". (He considers "arthritis" of many types all one disease. The types are not differentiated, hence no conclusions can be drawn—Ed.)

3 Infected sinuses. Infected sinuses including "silent sinusitis" are rarely a focus in arthritis according to some, not uncommon according to others^{103, 300}. Conservative treatment should be thoroughly tried before operation²⁸².

4 Nasopharyngitis of the diffuse type, even in the absence of tonsils may act as a focus (Willcox³⁰⁰).

5 Gall-bladder. That an infected gall-bladder may be the sole causative focus in arthritis, Patterson³⁰⁵ concluded from observations on one patient who noted prompt relief on two occasions once after an appendectomy and (presumably) a cholecystostomy (with subsequent relief for eight years), and again after cholecystectomy. Nonhemolytic streptococci

were found in the gall-bladder, a vaccine of which produced joint symptoms (Although prolonged remissions were obtained after both operations it is still possible that relief was due to a non-specific postoperative effect—Ed)

6 Uterine cervix, and prostate gland Infection of these is in most cases responsible, according to Robinson³⁰⁶ for arthritis He noted consistent improvement only when these (and not other infected foci) were treated "There is no remedy for it except (long-wave) diathermy given intrapelvically by special electrodes"

7 Secondary colon infections These according to some^{293, 300} are frequent, according to others rare³⁰⁷ Their importance is often exaggerated

Bacterial Vaccines, Antigens, Filtrates Of those writers who have recently expressed an opinion on vaccines, about 60 per cent have favored their use, 40 per cent have not Milliken³⁰⁸ gave to 25 patients with "chronic arthritis" a mixed vaccine (streptococci from blood, tonsils and colon added to Clawson and Wetherby's vaccine) An average of 36 injections was given over an average period of four months Systemic reactions were avoided, small doses used Patients were treated until they remained symptom-free for at least 30 days "Complete relief" was obtained by 12 patients (48 per cent), the average duration of their disease was 30 months "Moderate relief" was obtained by eight patients the duration of whose arthritis averaged 69 months Five patients (20 per cent) who had had the disease on an average of 106 months received little or no relief The best results were obtained in early cases and by those with the greatest tolerance for the vaccine (No other treatment was mentioned The series is very small, no controls were used, and the "arthritis" was undifferentiated—Ed)

Intravenous injections of streptococcal vaccine from strains to which patients were "skin-sensitive" were given by Wainwright²⁷⁸ to 45 patients, 30 (66 per cent) were "improved" Desensitization was attempted by using very small doses Constitutional reactions were avoided, but focal reactions in joints were common Improvement was slow but generally progressive and was first noted in four to six weeks Agglutinins increased, and skin-sensitivity diminished or disappeared The sedimentation rate was variably affected in those who improved steadily dropping in some, and remaining elevated in others despite definite objective and subjective improvement Hence Wainwright considered it of doubtful value as a test of improvement

Sherwood^{303, 309} reported further experiences with vaccines An earlier series consisted of 674 cases of "arthritis" ("atrophic or periarticular" 311 cases, "rheumatoid" 32 cases, hypertrophic arthritis 260 cases, gonorrheal 19 cases, and a few cases of neuritis and myalgia) About 60 to 70 per cent of patients in each group were "markedly improved" Treatment of four different types was "almost wholly with vaccines" Clawson and Wetherby's (Lilly Streptococcal Vaccine), Cutter's mixed respiratory vac-

cine, and two modifications of the latter. Results with each vaccine were about the same (Sherwood's "rheumatoid" cases were apparently those of early atrophic arthritis "with no bony change." No comparisons were made with patients treated by other methods than the use of vaccines—Ed.) Sherwood later treated 300 "arthritic" patients, of whom 100 each were treated with "Cutter's arthritis vaccine," with a casein solution, and with physiologic saline solution. Patients were assigned the solutions in rotation, the contents being unknown to the administrator. Within eight weeks (a very early time—Ed.) "marked improvement" was noted by two-thirds of those treated with vaccine, by half of those with casein, and by a third of those with saline; relief by the last-named measure was regarded as from mild psychotherapy.

Streptococcal vaccines were approved by several^{250, 251, 274, 307, 310}. Gray²⁵¹ found low complement in patients reacting unfavorably to minute doses. Various vaccines and antigens were given intravenously and subcutaneously by Boots,³⁴ Dawson,¹⁰³ Holbrook and Hill³⁰² without striking differences in results with different vaccines or in controls. They concluded that vaccines are of unproved value, generally harmless, have a psychotherapeutic value, and serve to bring the patient to the physician's office for more important therapy and control. Results vary with the enthusiasm of the user. Kinsella's³³ results were "unimpressive." Of 21 European physicians who had used "specific vaccines" Slocumb³⁰ found only nine who were continuing them. Yater²⁹⁹ thought that general practitioners should not be encouraged to use vaccines for arthritis lest they neglect more valuable methods.

Long-continued vaccine therapy was considered by Reiman and Eklund³¹¹ to be the cause of amyloidosis in the case of a young arthritic who died of uremia after having received 41 injections of vaccine in 22 months. His blood protein was 4.71 gm, albumin 0.74 gm, globulin 2.67 gm per cent, fibrinogen 1.29 gm per 100 cc.

(Parker and Keefer²³⁶ noted amyloidosis as part of the secondary pathology of the disease. Therefore, the disease and not the vaccine may have caused amyloidosis—Ed.)

The failure of autogenous vaccines to help more than 48 per cent of their patients led Lamb, Anderson, and Nerb³¹² to use filtrates (antivirus) of autogenous streptococci to which patients were "skin-sensitive." Of 70 patients with atrophic arthritis, 13 per cent "recovered," 36 per cent "greatly improved," 36 per cent improved slightly, 15 per cent were unimproved.

(No controls treated without vaccine or filtrates were studied—Ed.)

Intravenous doses of urinary proteose from arthritic patients gave no encouraging results (Kinsella³³).

Foreign Proteins. The actions and uses of, and contraindications to foreign protein therapy were reviewed by Hektoen³¹³ and Cecil²³⁴ who

regarded this treatment in selected cases as distinctly useful even if not brilliant. It generally does no harm although it may do no good. Cecil believed that foreign proteins should always be tried in acute arthritis unrelieved otherwise. Many of his early patients with atrophic arthritis "remained well" thereafter, many with chronic arthritis were definitely improved. Other authors^{34, 103} considered it of doubtful value.

Diet Pemberton²⁵³ again stressed the value of a diet adequate in proteins, vitamins, and calories, but with a reduction of concentrated carbohydrates. "There is some evidence to suggest that in selected cases a difference of 300 calories might turn the scale in favor of retrogression or improvement." He and Scull^{314, 315} considered that the value of their diet was explained by the fact that one of the dynamic pathologic changes in atrophic arthritis is a disturbance of water distribution in tissue, exemplified by the common appearance of edema in periarticular tissues. Their diet tended to provoke a negative water balance, which reduces swelling and inflammation.

(These water-balance studies were calculated only semi-quantitatively. The total acid-base balance and the insensible perspiration were not fully determined.—Ed.)

Considering the edema of arthritis as due to a low plasma albumin, Davis²⁹ regarded protein restrictions as harmful. A generous intake of protein may lessen the edema.

To correct supposed hepatic dysfunction in atrophic arthritis Todd²⁰⁰ "spares" the liver by prohibiting all fats (except butter and oils) and lactalbumin. (No acceptable proof of the need or value of this diet was given.—Ed.)

A diet high in "protective foods" (fresh fruits and vegetables), but moderately low in proteins and calories and low in carbohydrate, was used by Langstroth³¹⁶. Others thought that a low-carbohydrate or low-protein diet did more harm than good (Boots³⁴). Lookie²⁹ found restriction of carbohydrate of no merit and excesses of carbohydrate apparently not harmful, several patients continued to improve despite a daily intake of 500 gm for 15 to 65 weeks. The administration by Hensch²⁹ of 400 to 600 gm of carbohydrate daily for many weeks to patients whose atrophic arthritis was temporarily inactivated by jaundice did not counteract the analgesia with jaundice nor bring out symptoms of arthritis. Studies by others (Bauer,²⁰⁴ Hall and Myers²⁹²) did not indicate any abnormality in carbohydrate utilization or suggest that excess carbohydrate intake was an important factor. They saw no theoretical or clinical value in a low-carbohydrate diet.

(Our opinion is divided on this point. The majority agree with the foregoing views. Others believe that disturbed nutrition forms the background of much ill health from infection and that almost all nutritional deficiency states are best controlled by carbohydrate restrictions. Hence, they favor the view that nutritional disturbances are a causative factor in atrophic arthritis.—Ed.)

The majority favor no particular dietary restrictions, prescribe a generous intake of food except when reduction of the trauma due to obesity is

required, and believe that most patients do badly on prolonged dieting or starvation^{29, 34, 106, 291, 294, 301, 302, 310}

Excess feeding of vitamin C was advocated by Rinchart²³¹, improvement in capillary resistance tests (an index of latent scurvy) and in joints was noted. However, such feedings by Faulkner²²⁰ for four weeks were not helpful. Some believed vitamin deficiency played no rôle in the disease^{292, 294}. The results obtained by Bauer's patients²⁹ who adhered to a high-vitamin diet for three to five years were no better than those seen in his patients who had not been so treated.

For weak patients, a high-calorie diet and insulin just before meals are prescribed for a month by Copeman³⁰¹ (15 units once daily) and by Eaton³¹⁷ (5 to 20 units three times a day).

Additional Intestinal Therapy Colonic irrigations are still recommended by some, and condemned by others^{34, 252, 293, 299, 318}. The reported abnormalities in intestinal configuration were not found in 50 cases by Lang²⁵⁰. There is no evidence that these "abnormalities" (if they really are abnormalities) are related to atrophic arthritis. Possibly they result from (any) chronic illness^{279, 294}. Wyatt³⁰⁷ found no consistent evidence of faulty elimination. Cathartics can be replaced by exercise, regular habits, diet, and simple lubricants.

Iron, Blood Transfusion Only two of 21 anemic patients of Collins²⁶⁸ responded well to massive doses of iron. Transfusions may improve those with acute or subacute arthritis, with or without anemia, but are of little value in chronic afebrile cases^{251, 301, 302, 307}. Intragluteal injections of leukocyte extract improved Hartung's patients²⁹.

Miscellaneous Substances Cinchophen derivatives are very useful drugs which have been condemned unjustly, according to Snyder²⁹ and Eaton³¹⁷ who noted no significant toxicity therefrom. In the present state of our knowledge no endocrine therapy is specifically indicated¹⁰³. Nadler³¹⁹ warned against the use of dimithiophenol in arthritis, peripheral neuritis and multiple joint pains may result.

Gold Salts Gold salts are given in various preparations, solganol (aurothio-glucose), allochrysin (sodium aurothiopropionol sulphate), myoral, sanochrysin, myochrysin (gold sodium thiomalate), gold thioglycolate, or gold sodium thiosulphate (crisalbine). Some are given intravenously, others intramuscularly in aqueous solution or oil suspension. Colloidal gold, gold chloride or gold cyanide are ineffective (Forestier⁴¹). Contraindications to gold are the presence of severe diabetes, nephritis, hepatitis, marked hypertension or hemorrhagic tendencies. Doses are usually given weekly until a total of 15 to 2 gm is given. Some give only one course, but Forestier stated "no case of rheumatoid arthritis has ever been cured by a single series of injections." According to him at least two courses are always necessary, with an interval of not more than six to eight weeks between.

Many patients are sensitive to gold and reactions are common. Focal

reactions include increased joint pain and swelling. Mild general reactions include fever, urticaria, pruritus, "gold bronchitis or flu," herpes. They may not necessitate cessation of treatment. Severe and occasionally fatal reactions may occur as skin and mucosa, liver, kidneys and blood cells are affected. Symptoms are erythematous rashes, occasionally exfoliative dermatitis, albuminuria, hematuria, or acute nephritis with uremia, stomatitis, jaundice and severe hepatitis, iritis, vomiting, hiccough, and diarrhea (Abdel-Sayed,²⁶² Foestier,⁴¹ Hartfall and Garland,³²⁰ Holmes,³²¹ Slocumb,⁹⁹ and Slot⁴²). Agranulocytosis and fatal hemorrhages have been noted (Poynton²²⁰). One patient was delirious for two weeks (Abdel-Sayed²⁶²). Holmes³²¹ heard of two fatalities and had one patient recover from severe dermatitis. Of 100 patients treated by Hartfall and Garland three died of exfoliative dermatitis. Sixteen of 21 "rheumatic" patients treated with gold developed, after one or two injections, punctate basophilia and polychromatic blood cells which sometimes persisted 10 months.³²² In spite of these marked and even fatal reactions, however, some frankly considered gold the most effective treatment of the disease.^{41, 12, 320} Gold must be given carefully to selected patients by physicians alive to its dangers. Of Abdel-Sayed's²⁶² 14 patients, six were "cured," five improved. Of 100 patients of Hartfall and Garland's³²⁰ 70 per cent were "apparently cured or markedly improved." Pemberton³²³ (Liverpool) treated 69 patients 18 per cent were cured, 40 per cent much improved, 32 per cent improved. Foestier⁴¹ treated 550 patients, "between 70 and 80 per cent responded favorably." Fifty per cent of patients with early arthritis and 20 to 30 per cent of those with old arthritis were "apparently cured" by two to five series of injections, and they remained so for two or three years without other treatment.

(None of the editors has used this method. Untoward reactions have appeared often enough to make one very conservative regarding it. No other current non-surgical treatment for arthritis (including fever therapy) has a mortality of 3 per cent, which is that of one series. Results would have to be unquestionably superior to warrant this risk. No control series were reported by most of the writers. Many patients had supplementary treatment which was frankly discounted—Ed.)

Sulphur It is claimed that injections of colloidal sulphur elevate the cystine content of nails to normal, reduce the sedimentation rate, and improve the joints in the majority of cases. Sulphur is injected intramuscularly, intravenously, or both. Rawls, Giuskin and Ressa²⁸⁴ treated 200 patients with "arthritis." Some who did not respond to small doses (10 mg twice weekly) obtained results from 20 to 30 mg twice weekly. A few showed evidence of an overdosage after intravenous but not after intramuscular injections, the symptoms being fatigue, headache, drowsiness, anorexia, and increased joint pain. Greater toxicity temporarily developed in a few cases: urticaria and erythema, nausea, vomiting, cramps, diarrhea, and chills and fever, however, these soon disappeared. Of 33 patients with

atrophic arthritis, 15 were "improved" Those with a low cystine content of the nails received the most benefit Some were previously given a placebo (Ringer's solution intravenously) for six to eight weeks, improvement with sulphur was greater

Wheeldon²⁵⁵ treated 892 patients with "chronic arthritis" with sulphur He reported results in 25 cases each of atrophic and hypertrophic arthritis resistant to other therapy Each patient received 40 intravenous and 40 intramuscular injections of "Sulfur-Diasporal" "Every case improved subjectively" Muscle spasm was reduced in 85 per cent, and joints became smaller in 65 per cent, many becoming more movable Detailed studies were made on the physiologic effect of sulphur on the cystine content of nails, sedimentation rate, blood count, sugar and calcium, urinary indican, blood pressure and weight

Woldenberg^{285, 286} treated 231 patients with atrophic arthritis "Every case showed excellent clinical improvement" Best results were from 30 mg of colloidal sulphur (Sulfur-Diasporal) intravenously daily for 10 days "In the majority of cases patients were free from pain after five or six injections" Sometimes in acute cases a dose of 30 mg intravenously "completely rid the patients of the intense pain they were suffering within 36 hours of the first injection" "So far as we know no recurrences of the disease have taken place" (It is difficult indeed to believe these extravagant statements, particularly in view of the more conservative reports of others The patients also received physiotherapy daily No control series was observed and no details of the follow-up are given—Ed)

Of 11 patients who were given an average of 60 cc (600 mg) of colloidal sulphur (sulisocol) intravenously by Sashin and Spanboch,³²⁴ six "improved," five did not No conclusions were drawn McCarty³²⁵ found sulphur "helpful in a small series of cases" Todd²⁹⁰ approved such therapy However, Kinsella³³ noted no definite improvement in 50 to 60 patients, and in 12 cases of Dawson¹⁰³ it was "absolutely without effect"

Choline and Histamine These substances are being applied by iontophoresis to produce pronounced local and mild general vasodilation without the unpleasant systemic reactions from their parenteral use After iontophoresis with mecholyl (acetyl beta methylcholine chloride) such an effect lasted six to 10 hours, according to Abel³²⁶ who treated 11 patients with atrophic arthritis, 10 were "definitely improved" Two patients with Strumpell-Marie's disease were not benefited Kovacs³²⁷ regarded mecholyl iontophoresis the method of choice in the local treatment of small joints in cases of atrophic arthritis During iontophoresis the drug is actually absorbed, resultant physiologic effects on dogs were demonstrated by Kotkis and his associates³²⁸

Producing less vasodilation, mecholyl is inferior to histamine, according to Kling¹⁷ who tabulated reported results of histamine iontophoresis for "rheumatic affections" of 730 patients 84 per cent were "cured or improved" Kling treated 12 patients with "spondylarthritis and radiculitis",

seven improved Of eight patients with "sacroiliac arthritis" two improved, of eight with atrophic arthritis seven improved after 10 to 20 applications Treatments were sometimes repeated for recurrences of the disease Smaller joints responded better than large joints Copeman³⁰¹ approved the use of histamine by subcutaneous injection as well as by iontophoresis For unstated reasons "active rheumatoid arthritis" was considered a contraindication Levant³²⁰ checked the physiologic reactions of iontophoresis with histamine against that with controls (tap water and four other solutions) All produced superficial hyperemia, but therapeutic results were obtained only with histamine Several patients with "arthritis" were benefited (In most of these papers the classification of arthritis was completely inadequate Practically no control studies were made on patients treated otherwise—Ed)

Harpuder³³⁰ demonstrated the production of vasodilating substances (histamine and acetylcholine) in the skin during physical therapy

Concentrated Viosterol Vitamin D in Massive Doses Two arthritic patients on massive doses of vitamin D for hay fever, as prescribed by Rappaport and Reed (1933, 1934), noted improvement in their joints Dreyer and Reed³³¹ therefore gave similar large doses to arthritic patients Of 34 patients with atrophic arthritis, 25 were "improved" Patients with hypertrophic arthritis and with "arthralgia" were also improved Improvement was first noted, in some cases, after a week, in others after six months' treatment The disease was apparently "controlled," not cured, for although many became symptom-free and had no recurrences in 18 months, others had mild recurrences when administration of the drug was stopped Patients were given doses of 200,000 USP or international units of vitamin D (concentrated viosterol) daily for one month If relief was noted the dose was never increased, otherwise, the dose was increased by 50,000 to 60,000 units each week until improvement or overdosage was noted In stubborn cases patients were given 600,000 to 1,000,000 units daily for a few days and then put back on 200,000 units daily The majority received relief on 300,000 to 500,000 units daily

Tolerance of patients to the drug varied greatly Toxicity occurred more often after prolonged use of smaller, than the short use of larger, doses Symptoms of toxicity were persistent nausea, frequency of urination (with or without polyuria), lassitude, anemia, polydipsia, diarrhea, vomiting, and abdominal pain Blood calcium sometimes rose to 25 to 30 mg per 100 cc often without symptoms To prevent or combat toxicity, 6 gm of brewers' yeast were given three times a day with frequent success When signs of toxicity appeared, administration of the drug was discontinued for two weeks with disappearance of symptoms Then the drug was continued in nontoxic doses Conclusions from studies on humans and animals were that concentrated vitamin D in the doses used is not hazardous if signs of early toxicity are recognized and the drug is stopped Persistence in administration might lead to permanent effects, even death

Patients on this treatment for two to five years for other diseases showed no hypertension or other ill effects (The report is conservatively written, but apparently controls were not studied. Since a "control" and not a cure was obtained, auxiliary treatment such as physiotherapy was advised. In a recent communication Reed²¹² stated that they are now using no more than 300,000 or 400,000 units daily. Vrtiak and Lang³³² have treated 20 patients with atrophic arthritis, 12 [60 per cent] were improved, 8 were not. Results were considered not unlike those with other methods and indicated that a conservative attitude toward such therapy should be adopted.—Ed.)

Rest and Movement The virtues of systemic rest have been stressed as the most important part of treatment^{251, 253, 333}. Prolonged rest in bed is necessary for acutely swollen joints, for which splints or casts may also be required to make rest absolute. In chronic cases the problem is not one of rest versus exercise but of rest and exercise. The patient may overdo on rest, with resultant atrophy and ankylosis, but the majority overdo on exercise to "keep the joints limber"^{307, 318, 334}. In chronic cases some exercises, including bed-exercises, are necessary to preserve joint function and muscle tone, but not that amount which causes more pain²⁵². Therapeutic exercises for various joints were described in detail by Coulter and Molander³³⁵.

Physical Therapy Medicines, vaccines, and diets for arthritis gain and lose their popularity but centuries of use have proved the value of physical therapy. Many physicians do not understand its advantages, hence there is a scarcity of trained physiotherapists. In Massachusetts there are about 22 arthritic patients for every physician, but about 70,000 patients receive no treatment whatever (Ober²⁹). Physiotherapy is justly or unjustly held in disrepute for reasons listed by Behneman³³⁶. Indications for, and methods and results obtainable by physical therapy have again been reviewed^{337, 338, 339, 340, 341, 342}. Whenever possible the arthritic patient should receive physical therapy in three ways: (1) by daily home measures used by the patient himself^{335, 343}, (2) professional physiotherapy three or more times a week from technicians or physicians trained therein, and (3) annual or semi-annual visits to a spa or other institution for treatment combined with the advantages of a vacation (Aldred-Brown,³⁴⁴ Holmes,³⁴⁵ and Lautman³³³).

To supplement the limited sessions of professional physiotherapy which patients can afford, the intelligent ones and their relatives should be fully instructed in simple home methods. Thus the cost of the patient's care can be reduced and the physician can control the patients over long periods necessary for treatment. By demonstrations and mimeographed sheets Coulter²⁹ teaches his patients optimal types and amounts of heat, massage and exercises, and the use of cheap but effective electric bakers, whirlpool baths and appliances for harmless exercises.

(Few spas attempt to teach patients simple home methods of physical therapy which would permit their advantages to be projected into the patient's home environment. Seventy-five per cent of patients seen by one of us had previously consulted

cultists, generally because little or no physiotherapy was prescribed by physicians Unless the better types of professional and home physiotherapy are more fully utilized by physicians, patients will continue to flock to the spine and foot twisters —Ed)

Before "home-physiotherapy" can be safely prescribed, physicians themselves must learn its principles and methods, and when it is given it should always be under a physician's general supervision (Ober³⁴⁶) Uses and physiologic effects of heat were thoroughly reviewed by Pemberton³⁴⁷ and Fox³⁴⁸ Diathermy, approved by many, may be harmful in cases of atrophic arthritis with much demineralization of bone, according to Holbrook and Hill³⁰² (No proof of this is given—Ed) Pelvic diathermy is particularly useful for pelvic foci of infection (Robinson^{306, 310}) Cold or hot Epsom-salt packs are often very analgesic³⁰² Hot paraffin packs deserve wider use^{302, 307} Thermal baths and douches, and Fango (mud) packs have their protagonists^{350, 351, 352} Short wave therapy for chronic arthritis was approved by several (Berry,^{353, 354} Bierman and Schwarzschild,¹⁸ Kobak,⁸⁰ Torbett,⁷⁹ Wilson^{355, 356, 357}) The effect of short wave diathermy is about the same as that of ordinary (long wave) diathermy, according to Kovacs,³²⁷ but the former can be used in regions where electrodes cannot well be applied Kling⁷⁸ tabulated reported results from short and ultra-short wave therapy for "chronic arthritis", of 146 patients 80 per cent were improved Of his own 29 patients 72 per cent were improved Results were best with the 23 meter wave

Heliotherapy is often harmful for patients with rather acute arthritis or with fever Dizziness, nausea, vomiting and fever may result (Holbrook and Hill,³⁰² Jones³³⁴) Massage is over-rated and alone is useless, according to Jones³³⁴, others stress its importance Physical exercises can be reproduced easily and painlessly by sinusoidal currents³³⁴ Underwater therapy offers an unequalled means of preventing and correcting adhesions and of increasing muscle and joint function^{333, 358 359, 360} Occupational therapy has special advantages distinct from those of physiotherapy³⁶¹

Roentgen Therapy Results of roentgen therapy in "acute and chronic non-specific infectious arthritis" were "gratifying" according to Garland,⁴⁰ although not as striking as in gonorrheal arthritis Nine patients with "acute infectious arthritis" were treated four became symptom-free, two improved Of 13 patients with joints irradiated in these cases, six became symptom-free, two improved Three patients with "chronic infectious arthritis" were treated two became symptom-free Of 10 joints treated, three became symptom-free, six improved Scott³⁶² approved radiotherapy, but King³⁶³ considered it of little value An analgesic, not a curative effect, is more frequent in acute than in chronic cases

Fever Therapy Results of fever therapy for atrophic arthritis have been satisfactory to some (Kobak⁷⁴), disappointing to the majority They are not nearly as good as in gonorrheal arthritis Hensch, Slocumb and

Popp⁴⁸ tabulated results given in the first 15 reports thereon (1931-1934) of 147 patients, only 7 per cent were "cured" or completely relieved. Of 60 patients treated by Hench, Slocumb and Popp, none was cured, 18 per cent were markedly, and 12 per cent moderately benefited, and 70 per cent received little or no relief. At the Fifth Annual Fever Conference (May 1935) results in 129 more cases were reported (Hefke,^{45 51} Stecker,⁴⁵ Strickler,^{45, 53} Tenney and Snow⁴⁵). Summarizing all published reports, the earlier optimistic and later conservative ones, Hench⁵⁶ found that of a total of 315 patients with chronic atrophic arthritis treated by fever, only 5 per cent became symptom-free, 25 per cent were notably relieved, but the rest received little or no relief. Results were a little better in cases of acute atrophic arthritis: of 21 patients, 10 per cent seemed completely relieved, 40 per cent notably benefited.

Recently Short and Bauer⁵¹ gave 71 fever sessions with general diathermy to 25 patients, 80 per cent showed temporary improvement, but in only 20 per cent was this maintained until the follow-up 6 to 41 months later. None were harmed but all looked on it as a harrowing ordeal. Balancing results against the treatment's severity, Short and Bauer concluded that it was only occasionally justified and should not be used to the exclusion of other treatment. Rogers³⁶⁴ noted benefit in one case. The use of low temperatures (101° F. for 3 to 5 hours) was recommended by Atsatt and Patterson^{47, 73}. Simpson⁴⁵ and Shands⁴⁵ felt that artificial fever therapy given just before or after orthopedic manipulation of deformities increased the results of manipulation.

Malarial (fever) therapy was given to 13 patients by Cecil, Friess, Nicholls and Thomas³⁶⁵. All received immediate, sometimes striking, benefit, but, six months later, only one was symptom-free, a patient whose arthritis was of only four months' duration. In 12 cases the arthritis relapsed, in eight completely, to its original state, in four partially. (One of us, P. S. H., gave malaria to a patient with severe atrophic arthritis in 1928; only a temporary, partial remission resulted.—Ed.)

Surgical Procedures 1. Sympathectomy. Sympathectomy was performed in five cases of "chronic arthritis" with hyperhidrosis and vasomotor disorders in affected limbs. Results were reported by Ross³⁶⁶. Two of three patients whose arms were affected "derived great benefit". In one of two patients whose legs were affected "the treatment was successful in relieving pain and restoring function" (No further details were given). De Takats³⁶⁷ considered sympathectomy of unproved value in chronic arthritis. In an unstated number of Boots' cases,³⁴ poor, as often as good, results were obtained. Unilateral lumbar sympathectomy was performed by Kinsella³⁸ in "about 35 cases" to study results on one leg. The first results were very good, but subsequent results did not justify continuance of the procedures. Relief of pain and increase of motion were not constant. Several papers on physiologic reactions after sympathectomy are of interest.^{368 369 370 371, 372}

2 Splenectomy was recently performed in two cases of "Felty's syndrome" (Hanrahan and Miller, 1932, Craven, 1934), only temporary improvement was noted. Miller and Craven have since notified Fitz²⁶ that the patients died 14 and 18 months after operation.

3 Thyroidectomy is said to benefit the joints of arthritic patients with hyperthyroidism. (This relationship has been discussed previously—Ed.) Bach²⁰⁷ noted marked improvement in one case immediately after operation.

4 Parathyroidectomy. Also previously mentioned was the supposed relationship between the parathyroid glands and polyarthritis and the reported relief of arthritis by parathyroidectomy. Schkurov²⁹⁸ performed this operation in 83 cases of "chronic rheumatic polyarthritis and spondylarthritis." The results and other reports concerning arthritis and the parathyroids will be discussed later.

5 Orthopedic procedures. Synovectomy is done by some orthopedists for active polyarthritis, by others only for persistent monoarthritis of knees unresponsive to other treatment. Radical synovectomy of knee joints may remove an infected focus and pathologic debris which interferes with partial restoration of function. Ankylosis rarely supervenes. Restoration of considerable function resulted in the few cases currently reported^{15, 19, 252, 273, 374}. Several reviewed the indications, methods and results obtainable by various procedures for the correction and prevention of deformities: traction, casts, splints and supports, tenotomies, osteotomies, capsulotomies, arthroplasties, fusions, manipulations^{10, 20, 21, 102, 153, 318, 331, 371, 375, 376}. Manipulation is particularly emphasized as a valuable method used insufficiently^{19, 318, 377, 378, 379}. Reconstructive surgery is not indicated until the arthritis has been inactive at least six months³⁸⁴. A chain for patients with bilateral ankylosis of hip joints was described (Kuhns³⁸⁰).

Prognosis, Remissions and Results of Treatment. A patient with atrophic arthritis (or any other kind) will follow one of four life courses according to Nissen³⁸¹. Of 500 cases of arthritis studied by him from the onset of the disease until the patient "ended with 'hic jacet'," 208 cases were classified "rheumatoid-genuine arthritis with actual destruction, partial or complete." Of these cases only 2 per cent followed course A (an initial attack and full recovery to the former level of activity), 32 per cent followed course B (remissions, relapses, and a slow steady decline in functional activity), 56 per cent followed course C (a drop to a low level of functional activity in a variable period of time, the patient remaining at that low level for the rest of his life), 10 per cent followed course D (a steady downward course from the onset of disease to death).

According to Dawson¹⁰³ about 25 per cent of patients "recover," 50 per cent "improve" or their condition becomes "quiescent," and 25 per cent become progressively worse. Of Pemberton's²⁵³ 300 patients with atrophic and hypertrophic arthritis (types not analyzed separately), 6 per cent were "cured," 32 per cent "greatly improved," 57 per cent "definitely improved."

"The figures were almost exactly the same for both the atrophic and hypertrophic types of arthritis." Results for Lang's²⁵⁰ 100 patients were 60 per cent improved, of which 43 per cent were "markedly improved." The patient's cooperation in treatment is of paramount importance. Of those who improved markedly, 90 per cent were persistent and cooperative in treatment, of those who did not improve, 64 per cent were uncooperative, discontinuing treatment within six months.

As a rule atrophic arthritis becomes inactive relatively slowly (within weeks or months) even under the most successful treatment. Neither preliminary nor final remissions appear abruptly within a few hours. Particular significance may therefore be attached to the dramatic sudden remissions that may accompany intercurrent jaundice. Hench (1933-1934) reported the "analgesic effect" of intrahepatic jaundice on 16 patients with atrophic arthritis, fibrositis and sciatica. Since then he has studied many more such cases in which sudden remissions accompanied jaundice of different types.⁴⁰ An example was given: a woman aged 49 years, had periarticular fibrositis and atrophic arthritis for three years, which developed so that she was unable to turn a doorknob, squeeze a wash cloth, or grasp a tumbler. A febrile laryngitis developed for a few days. Ten days later she awoke to find herself jaundiced and completely free of all signs and symptoms of rheumatism. Details concerning the physical and chemical examinations during the remission were given. For several months the patient was completely free of symptoms, then the disease began to return. In the majority of such cases the remission was complete and lasted weeks or months, occasionally longer. These observations indicated to Hench that the clinical pathology of atrophic arthritis is probably much more reversible (and more rapidly so) than was heretofore evident, and led to the hope that an intensive study of this phenomenon may eventuate in a method of treatment similarly dramatic and prompt.

HYPERTROPHIC ARTHRITIS

Definition. Most roentgenologists who see any overgrowth of bone in roentgenograms in a case of articular disease make a diagnosis of "hypertrophic arthritis," and if bone overgrowth is absent, the diagnosis is apt to become "atrophic arthritis" (Pemberton²⁹). Radiologists must exhibit a more informed type of scrutiny and become familiar with the variable pathologic and clinical aspects of the different arthritides to interpret roentgenograms more correctly. The clinical definition of "hypertrophic arthritis" is (or should be) quite different from the radiologic definition of "hypertrophic arthritis." Roentgenographically there are several different types of hypertrophic arthritis, such as that seen in certain traumatized joints, or those types found in certain stages of gouty, gonorrheal, atrophic and other forms of arthritis (Haden,²⁹ Doub,¹¹ McMurray¹⁰). To the clinician, however, hypertrophic arthritis means (or should mean) one particular disease, one special type of arthritis. The various forms of arthritis in which the roentgenographic changes of hypertrophy of bone are

but a minor feature, an incident compared to more obvious clinical features (acute trauma, acute gout, gonorrhea, and so forth), might be called "secondary hypertrophic arthritis." Thus they are distinguished from "primary hypertrophic arthritis," the clinical syndrome synonymous with "senescent," "degenerative" or "osteo-arthritis" in which, in the absence of a known cause or more striking clinical features, roentgenographic alterations constitute the most consistent and outstanding feature of the disease and give it a name (Haden ²⁰)

Incidence Studies of knee joints of persons from the first to the ninth decade of life indicate that after the age of 30 years the degenerative changes that lead to hypertrophic arthritis were found with increasing frequency, so that by the fifth decade all knee joints were so affected (Keefer ³⁶² also 1933, 1934, Bauer and Bennett ²⁹ also 1933)

(Radiologic and pathologic studies by others have indicated that hypertrophic spondylitis is also present in practically all patients aged 50 years or more—Ed)

The sex incidence is about equal (Dawson ¹⁰²), but the fingers, knees and cervical spine are more commonly affected in women, the lower part of the spine and hips in men

Symptoms and Course Although the disease is almost universal in persons more than 50 years of age, only about 7 to 10 per cent of its victims have significant symptoms (Keefer, Parker, Myers and Irwin, 1933, 1934) Those with symptoms fall into three groups (1) the obese, whose traumatized weight-bearing joints early proclaim their hypertrophic arthritis, (2) mechanics and workers in occupations in which trauma elicits painful symptoms, (3) hypersensitive persons (generally females) whose pain perceptions are augmented (Hench ¹⁰⁶) Symptoms rarely appear before the age of 40 years, usually after the age of 50 They may appear before the age of 40 in females who have experienced a premature or artificial menopause or in persons subject to some unusual forms of long continued trauma (Dawson ¹⁰³)

Symptoms are not always confined to joints Just as every case of atrophic arthritis has some associated fibrositis, so in hypertrophic arthritis, fibrous tissue may share the pathologic process of degeneration (Howitt ²⁶³) Neuritic and muscle pains and stiffness ensue

(Symptoms of this senile fibrositis—fatigue, loss of muscular resiliency, chilliness and vague muscle pains—are so universally present in senility that Pennington, 1934, was of the opinion that "senility is practically synonymous with fibrositis"—Ed)

Small gelatinous cysts occasionally appear, attached to tendons near a Heberden's node (Hench ¹⁰⁶) They are often opened "to let matter out" This is generally unnecessary, they may recede spontaneously Occasionally they become inflamed After they are opened, the walls collapse and the unsightly nodule recedes, though it may reform

(These have escaped general notice and description. Photographs of them are in reports of Hench¹⁰⁰ and of Nachlas (1932). The latter studied 28 specimens thereof, generally over the terminal phalangeal joints of hands affected with Heberden's nodes. In one of Hench's cases the cystic nodule was over a midphalangeal joint. According to Nachlas the mucoid or gelatinous material therein may contain excess calcium in solution but no urates, and if unremoved, the nodules eventually solidify to form genuine bony Heberden's nodes—Ed.)

Röntgenograms Radiologic features were reviewed by Doub¹¹. As before noted, those seen in cases of "traumatic hypertrophic arthritis" in young persons subjected to severe acute or chronic trauma may resemble those of "senescent hypertrophic arthritis" (degenerative, osteo-arthritis) in relatively non-traumatized joints of the elderly (e.g., distal phalangeal joints). Cases of polyarticular "hypertrophic arthritis" are more likely to represent senescent hypertrophic arthritis than cases of chronic monoarticular "hypertrophic arthritis," as these latter may represent old traumatic arthritis, such as ensues in hips after Perthe's disease or osteochondritis or following slipped femoral epiphyses in childhood^{10, 11}. Thus the average age in McMurray's¹⁰ cases of bilateral hypertrophic arthritis of hips was 53 years, in cases of unilateral hypertrophic arthritis of a hip it was only 34 years and there was a frequent history of childhood injury. Therein lies further evidence of the necessity for distinguishing between the clinical syndrome of (senescent) hypertrophic arthritis, which is one disease, and "hypertrophic arthritis" in the radiologic sense which is not a disease per se but a radiologic feature of several diseases.

Pathology The articular pathology in hypertrophic arthritis, reviewed by Keefer³⁸² and Parker and Keefer²⁵⁶ was so different from that of atrophic arthritis that the idea that the two diseases are the same seemed untenable. Muscles, tendon sheaths and fascia, with their small blood vessels, also participate with joints in the general state of fibrotic thickening, according to Howitt²⁰³.

(The pathology of this associated "senescent fibrositis" is not described further. As has been done for joints, studies on the histology of muscle and fibrous tissue at different age periods should be made to clarify the pathology of senescent, as contrasted to other types of, fibrositis, and to explain the "stiffness of age"—Ed.)

Laboratory Data Marked anemia is not a feature of hypertrophic arthritis. Gray, Bernhard and Gowen²⁶⁹ found the erythrocyte count below 4,000,000 per cu mm in only 16 per cent, and the value for hemoglobin below 70 per cent in only 6 per cent, of cases of hypertrophic arthritis. Hemoglobin was normal (over 14 gm) in 11 of Collin's²⁶⁸ 23 cases, between 12 to 14 gm in 11 cases, below 10 gm in only one case. The Schilling count was shifted to the left (an increase in percentage of younger neutrophils) in only 17 per cent of Steinberg's²⁷⁰ cases of hypertrophic arthritis, but in 78 per cent of his atrophic cases. The percentage of younger neutrophils was less than four in most cases of the former, above four in most of the latter. There was a general correlation between Schil-

ling counts and sedimentation rates the latter were usually below 0.35 mm per minute in hypertrophic, above 0.35 mm in atrophic arthritis (Rourke and Einstene method) Gray²⁵¹ found the sedimentation rate (Westergren method) over 20 mm per hour in only 2 per cent, 10 mm or below in 85 per cent. Essentially similar rates were noted by others^{29, 34}

No relation between anemia and gastric acidity was found by Collins²⁶⁸, only one of 11 cases had reduced gastric acids. Of 35 cases, achlorhydria was found by Hartung and Steinbrocker²⁷² in 26 per cent, hypochlorhydria in 3 per cent (subacidity was 17 per cent more frequent in atrophic arthritis)

Values for total blood protein, globulin, albumin and plasma fibrinogen were normal in Davis'²⁹ cases of hypertrophic arthritis (generally abnormal in atrophic arthritis). Alterations in blood proteins were found by Aldred-Brown and Munio²⁶⁷ when patients with hypertrophic arthritis (group 1) were compared to healthy young normals (group 2), but these differences tended to disappear when they were compared to non-rheumatic persons of less favorable economic status (group 3). The average values (gm per 100 cc of plasma) were as follows. In groups 1, 2 and 3, respectively albumin 3.91, 4.51, 4.09, globulin 2.32, 1.69, 2.13, fibrinogen 0.34, 0.16, 0.22, total protein 6.35, 6.37, 6.35. Thus plasma protein was low in hypertrophic, but not so low as in atrophic, arthritis.

Hartung and his associates^{258, 259} found a tendency towards an elevated plasma cholesterol and a lowered serum calcium. Of 59 cases, 62 per cent had high, 3 per cent low, and 35 per cent normal, values for cholesterol (160 to 230 mg). The mean total cholesterol was 235.4 ± 45 mg. Values for the mean and standard deviation of serum calcium were 9.986 ± 0.616 mg per 100 cc (normal 10.241 ± 0.647 mg). Race²⁶⁰ noted a slight but definite tendency towards lower values for serum calcium in atrophic than in hypertrophic arthritis. Serum magnesium was essentially normal in hypertrophic and atrophic arthritis (a little lower in the latter). Blood groups were as in normals. There was no characteristic deviation in urinary acidity.

Etiology and Pathogenesis Various writers have blamed each of the following factors as the sole cause of the disease: heredity, constitution, the degenerative processes of age, chronic trauma, circulatory disturbances, some specific metabolic fault, an endocrine disturbance, infection. Others believe that not one factor, but a combination of factors is responsible—particularly age plus chronic trauma. Still others believe there is one specific cause, as yet unknown, and that those mentioned are merely predisposing, precipitating, or accelerating factors of secondary importance.

Factor of Heredity and Constitution Heredity is commonly blamed because patients state the disease "runs in the family."¹⁰³ Its incidence, however, is so general that practically all one's ancestors over 50 years of age had it. Others blame heredity not for the disease's general incidence as much as for its premature appearance. "Some patients inherit better cartilage than others. The poorer the inheritance and the greater the endogenous

and exogenous trauma, the earlier will hypertrophic arthritis develop" (Bauer and Bennett ²⁹) Pribram and Fahlstrom ²⁶¹ are current sponsors of the idea of a constitutional tendency of brachymorphics for the disease, but many of Pemberton's ²⁵³ patients were slender

Factor of Tissue Degeneration (Tissue Age) One's calendar and histologic ages are of course not identical. Furthermore, because of differences in the histologic "ages" of various organs, one's mental (cerebral) and general physical ages may be quite different. The majority believe that the histologic age of cartilage (age being the sum total of all traumatic and toxic insults of life) is the chief determinant of the disease. Hypertrophic arthritis represents a localized, premature senile change which may occur in clerks as well as bricklayers, from mental as well as physical overstrain (Howitt ²⁶³)

Factor of Trauma To some, "age" is but the sustained opportunity for mild long-continued articular trauma as a result of posture, obesity, occupation or recreation. They regard the disease as the result of such chronic trauma, or that from intra-articular or juxta-articular fractures with faulty alignment, unreduced dislocations, foreign bodies or other orthopedic disabilities ^{13, 279, 283}. Doub and Jones ¹² related the disease to chronic but not to acute trauma since single severe trauma (juxta-articular fractures) seemed to play no rôle in the production of hypertrophic arthritis.

Factor of Circulatory Alterations Circulatory deficiencies (arteriosclerotic, inflammatory, or vasospastic) leading to excess articular catabolism have been held responsible. However, no evidence is at hand that the nutrition of a person's osteo-arthritic joints is more deficient than that of his unaffected joints, or that there is more arteriosclerosis of nutrient vessels of the former than of the latter ¹⁰³.

Factor of Altered Metabolism In contrast to the idea of a nonspecific metabolic defect from poor articular circulation is the theory that some more or less specific metabolic derangement is responsible, a disturbance in utilization of sugar, of calcium, of sulphur. A defect of the last type is now a popular notion, and some believe that hypertrophic as well as atrophic arthritis is due to a deficiency of sulphur in the body, particularly in cartilage ^{255, 284-286, 288, 289}. The majority have made no attempt whatever to differentiate the types of arthritis in which they found reduced cystine in nails or which improved on sulphur—merely labelling them "arthritis" or "chronic arthritis". Wheeldon ²⁵⁵ noted that the average cystine content of nails was a little lower and rose higher after treatment in hypertrophic, than in atrophic, arthritis. Senturia ²⁸⁷ found no abnormal urinary excretion of sulphur in either type.

(It is impossible for a critical reader to form any conclusions when even the types of arthritis treated are not differentiated—Ed.)

Some are still keeping alive the notion that the disease is related to a purine disturbance since "the blood uric acid is always increased" ²⁹⁵. (This has long since been disproved by numerous careful investigators—Ed.)

Todd²⁹⁰ "slightly" incriminated "the hepatic factor," and Miller²⁹¹ noted hepatic dysfunction (an altered levulose tolerance) as often in hypertrophic as in atrophic arthritis (in about a third of each group)

No causal relationship between hypertrophic arthritis and any metabolic disturbance associated with diet was found by Bauer²⁹⁴ or by Hall and Myers²⁹². According to Langstroth³¹⁶ the relationship of the disease to diet is a paradoxical one, although there is no evidence that its victims have eaten less "protective foods" than others, the administration of such foods is of value

Factor of Endocrine Disturbances Although the disease frequently becomes symptomatic near the menopause, no definite connection between it and endocrine glands has been proved. Since hypertrophic arthritis occurred in only 17 per cent of 414 cases of hyperthyroidism, no relationship between these two diseases was apparent to Monroe²⁹⁰. However, of 98 patients with myxedema, 33 per cent had hypertrophic arthritis, "an intimate and important association". Their average age was 51 years, but myxedema and not just age was considered the major factor

Of Haden's²⁹ 50 cases of hypertrophic arthritis, a "low" metabolic rate was found in 84 per cent, an accelerating factor considered important

(Many others, e.g. Race,²⁹⁰ considered metabolic rates to be normal—Ed)

Factor of Infection The factor of infection seems unimportant to the majority²⁹. There is little or no direct evidence of infection, and various immunologic reactions used as evidence of the infectious nature of atrophic arthritis are usually absent in hypertrophic arthritis. Blood cultures by Gray²⁵¹ in 79 cases were all negative for streptococci. Agglutinins to hemolytic streptococci were not found by Dawson¹⁰³. They were rarely found by Gray, Bernhard and Gowen²⁶⁰ in significant amounts (1:160 or higher) they were present in low titer (0 to 80) in 83 per cent of cases, in a titer of 160 to 320 in 17 per cent, none in higher dilutions. In only three of Blair and Hallman's²⁹⁰ 16 cases were agglutinins to Cecil's "typical" streptococcus found in dilutions greater than 1:160. Antistreptolysins in abnormal amounts (over 100 units) were found in only two of 13 cases of "chronic arthritis other than rheumatoid". Skin reactions to hemolytic and green streptococci were absent in four, present in six cases of Wainwright²⁷⁸. One patient reacted to two strains, two patients to three strains and three to five strains or more

(No interpretation was offered—Ed)

Some believe, however, that infection plays a contributory rôle. Pemberton²⁵³ reported two cases: one patient responded "immediately" to the removal of infected teeth, suggesting that infection played a rôle, and the other to rest, diet and improved intestinal function, suggesting that age alone was not responsible. The difference between a painful joint with hypertrophic arthritis and a painless one roentgenographically even more hyper-

trophic, is generally thought to be the factor of trauma, but Sherwood³⁰³ agreed with Key (1933) that low grade infection may produce pain in joints which would otherwise be symptomless. Bauer²⁰ ascribed the variable presence of pain to changing pathology. When marginal osteoid tissue proliferation is occurring, periosteum may become elevated and pain results. When this osteoid proliferation ceases and the tissue becomes calcified pain may stop.

Treatment Perhaps the most important part of treatment is to explain to the patient the differences in the nature, particularly in the prognosis, of the disease he actually has from that which he thinks he has, and to assure him that hypertrophic arthritis (unlike atrophic, "deforming arthritis" which he fears) is not essentially an ankylosing, severely-crippling, progressive disease. This done, many patients neither ask nor accept other treatment but bear their difficulty philosophically without the "nuisance of treatment" (Hench¹⁰⁶).

Rest and Reduction of Trauma Many patients are deliberately over-exercising under the erroneous impression that "unless the joints are kept active they will stiffen." With the onset of symptoms of hypertrophic arthritis patients often go out of their way to activate the joints, "to keep limber," grimly determined to keep going. This only irritates the process and is harmful and unnecessary, as ankylosis is not characteristic of the disease. Generous rest and the reduction of trauma are highly desirable, although not to the extent that the patient feels himself a crippled invalid^{13, 106, 253, 283}. Extra hours of rest at night and in the daytime, reduction of obesity, and the use of a cane, corset or roller bandage, will minimize trauma and permit a patient to be comfortable when he is active.

Diet Reduction of tissue edema and relief by means of the mild, dehydrating effect of a low-carbohydrate, low-calorie diet were noted by Scull and Pemberton^{314, 315} in hypertrophic, as well as in atrophic, arthritis. Others found no special dietary indications for the disease except for the reduction of obesity^{292, 294}.

Removal of Foci This has seemed useless in the majority of cases, though it may be indicated in particular instances^{253, 304}.

Vaccines Vaccines are generally not prescribed. Sherwood^{303, 309} treated 260 patients with various vaccines with results which were considered as good as those obtained in atrophic arthritis.

(He stated that neither the severity of symptoms nor the type of arthritis influenced the results from vaccine. This experience is at variance with that of the majority and makes one doubt the value of the vaccine, particularly when a definite, if smaller [33 per cent], number of controls improved on saline injections—Ed.)

Young,³⁸³ an associate of Crowe, used the latter's vaccine "successfully" in treatment of 100 cases of "osteo-arthritis." Contrary to what is customary, their plan is one of progressively *smaller*, not larger, doses of vaccine. McCarty³²⁵ also considered (intravenous) vaccines helpful for pain, but less so than in atrophic arthritis.

Sulphur Relief from injections of sulphur was reported in hypertrophic as well as in atrophic arthritis²⁵⁵ Good results ensued "in every case" (five) in one series,^{285, 286} in 50 per cent of another series (26 cases),²⁸⁴ but in only three of eight cases in a third group³²¹

Gold Injections Such injections were used in the hypertrophic type also In a series of 17 cases, Pemberton³²³ (Liverpool) noted much improvement in 24 per cent, improvement in 13 per cent For intractable osteo-arthritis Slot⁴² combined the use of gold with epidural injections of procaine Foestier⁴¹ found gold of no value in osteo-arthritis

Iontophoresis with Vasodilating Drugs Of 25 patients treated with histamine by Kling¹⁷ 60 per cent improved Of 29 patients treated with mecholyl by Abel³²⁰ 90 per cent had relief of pain, Kovacs,³²⁷ however, noted no relief with mecholyl

Miscellaneous Thyroid extract was used by some¹⁰³ Relief of pain was obtained by Foestier³⁸¹ with local injections of lipiodol (perineural, peri-articular) Ten of 18 patients improved while on large doses of vitamin D (concentrated viosterol) (Dreyer and Reed³³¹)

Physical Therapy This, of course, is extensively advocated Underwater therapy is especially valuable for elderly patients with hypertrophic arthritis³⁵⁸ Some advocated short-wave therapy^{79, 354, 356} Diathermy was particularly approved by Kovacs³²⁷ Roentgen therapy was used by Garland⁴⁰ in seven cases of hypertrophic spondylitis only one patient became symptom-free but four "improved" Fever therapy is cautiously approved by some,^{47, 73} considered of no value by others,^{51, 74} Tenney and Snow noted improvement in only four of 10 cases³⁸⁵ Various other physicians have treated a total of 74 patients only 4 per cent became symptom-free, about 50 per cent noted some relief⁴⁸

Orthopedic Treatment Considerable relief may result from manipulation in selected cases, such as osteo-arthritis of the cervical or lumbar spine, or hip^{10, 318, 334, 377, 379} Synovectomy may help some patients greatly^{334, 373} Bone puncture (Mackenzie, 1931-1932) relieved a few, failed in other cases⁹⁹ Cheilotomy to remove femoral osteophytes has not been very successful and is inferior to hip joint resection³³⁴ Because bony union is difficult to obtain, arthrodesis is less useful than reconstruction of hip joints

BACKACHE AND SCIATICA

Backache and sciatica are not, of course, diseases per se but symptoms of many diseases The anatomic physiology of the spine and its adjacent tissues is so complicated that experienced orthopedists at times have great difficulty in determining the cause of backache or sciatica The physician without at least some orthopedic training is even more confused He is apt to examine the spine for rather gross stiffness, look for spurs in roentgenograms and, if there is a poker spine, the diagnosis becomes "ankylosing spondylitis" (or an equivalent term) If there are spurs the diagnosis

becomes "hypertrophic spondylitis" If neither is present the diagnosis becomes simply "backache" Going a little farther, he may offer a favorite explanation "backache due to poor posture," from "uterine displacement," from "strain" or "fatigue"

The literature reviewed contained about 50 articles on, and about as many classifications of, backache Backache can be briefly classified as being from (1) primary neurologic conditions, (2) genito-urinary disease, (3) gynecologic disturbances ("post-pregnancy backache," etc.), (4) metastatic malignancy, and (5) "orthopedic conditions" Commoner orthopedic conditions which produce backache are postural or occupational strain of muscles and ligaments, infections of ligaments, muscles and their fibrous tissue (toxic or infectious "myofascitis" or "paravertebral fibrositis"), developmental anomalies of the fifth lumbar and first sacral region, disturbances of the intervertebral disks, and (traumatic, infectious or degenerative) arthritis of the vertebral bodies or articular facets, or both

The lower back is a common site of symptoms in the malingerer, be it the industrial worker seeking compensation or the tired housewife seeking sympathy Points useful in detecting malingering were listed by Stuck³⁸⁶ To be determined are (1) an estimate of the patient's sincerity of purpose from his general demeanor, (2) whether his general body build and posture (tall, thin), or his occupation are such as to make him liable to injury, (3) a reasonable consistency between the severity of the injury and that of symptoms (In general there is a correlation between the two, although there are exceptions and trivial injuries may induce severe backache, and only mild damage may result from a violent accident), (4) the relationship between the time of injury and the onset of symptoms (as a rule symptoms appear within a few hours), (5) presence or absence of previous backache, (6) in the presence of organic disease examination will generally reveal muscle spasm, sometimes scoliosis, it being difficult if not impossible for a malingerer to feign muscle spasm or scoliosis except momentarily, (7) with organic disease, tender spots remain rather consistently localized during the first and subsequent examinations, malingerers rarely recalling the sites of previous "tenderness" carefully enough to avoid detection, and (8) the newer technic of making roentgenograms (Ghormley and Kirklin, 1934) will reveal disease of facets as well as of vertebral bodies

The technic and significance of various manipulative methods of examining the back to localize disease of the spine were reviewed by several³⁸⁶⁻³⁹⁶ Some considered the physical examination much more valuable in certain cases than roentgenograms because the latter may reveal changes (spurs, anomalies) which may or may not be related to the presenting symptoms Without careful investigation symptoms must not be too readily blamed on the hypertrophic lipping so commonly seen in laborers and in the obese over 40 years, and in others over 50 years of age

Comments on Differentiation Figures on the percentage of cases of

backache from arthritis are not always reliable as they are often colored by a physician's special knowledge or lack of it. If in a given case pelvic disease is present, a gynecologist may blame the backache thereon without seeking a further explanation, if pelvic disease is absent he may rightly or wrongly dismiss the case as of "rheumatic origin." The practitioner may blame poor posture in a case when roentgenograms of the spine are apparently "negative." (The word "apparently" is used advisedly as, too often, roentgenographic examination is limited to an antero-posterior view of the spine, and lateral and oblique ["three-quarter"] views are not taken—Ed.) Of 63 cases of backache seen by Shafiroff and Sava³⁹⁷ 70 per cent were from "arthritis," of which 50 per cent were ascribed to "traumatic arthritis of facets," 39 per cent to "lumbosacral and sacro-iliac osteoarthritis," and 11 per cent to "generalized arthritis." They concluded that in backache from pelvic disease the pain was likely to be diffusely spread over the back and referred anteriorly to the legs from pressure on iliohypogastric, ilioinguinal, and femoral nerves, but that in backache from osseous disease, pain is more localized to the affected area and is projected generally along the posterior portion of the leg from pressure on sacral nerves.

(The data given are inadequate for the reader to accept fully the diagnoses and differentiation—Ed.)

In differentiation Gotten³⁹⁸ characterized the pain of lumbosacral myositis as being usually aggravated by cold or damp and partially relieved by exercise, while that of arthritis is aggravated by exercise. Of the common types of backache—traumatic, infectious, and static or attitudinal—the last constitutes 90 per cent, according to Davidson and Horowitz,³⁹⁹ and frequently leads to microtraumatic arthritis. Certain differences were noted by Magnuson³⁹⁹. Pain which is worse in the morning on rising, but disappears after brief activity is frequently due to "peri-arthritis" of paravertebral ligaments and muscles, a condition which often causes night-backache, because of which a patient awakes to find a more comfortable position. A backache appearing in the afternoon or evening is more frequently due to fatigue, poor posture or arthritis.

(As generalizations these statements are fairly sound, but it must be remembered that many cases of spondylitis are associated with paravertebral fibromyositis, symptoms of which may dominate at times, in which case the patient may feel worse on rising, better after some exercise—Ed.)

The "Newer Anatomy" of the Spine Until recently studies on spondylitis dealt almost exclusively with diseases of the vertebral bodies and adjacent ligaments. In atrophic spondylitis (spondylitis ankylopoietica) the chief pathologic finding was regarded as inflammation and calcification of paravertebral ligaments, the vertebral bodies not being affected early except by atrophy. In hypertrophic spondylitis (spondylitis osteoarthritica) tipping of vertebral bodies was evident. So, too, in suspected traumatic spondylitis roentgenographic evidences of trauma were sought in

vertebral bodies, if these appeared normal pain was ascribed to traumatized muscles and ligaments. However, since the work of Schmorl (1927 et seq), Schmorl and Junghanns (1932), Beadle (1931), Ghormley (1931 et seq), Keyes and Compere (1932-1933) and others, major interest has been transferred to the anatomy and pathology of the intervertebral disks and "paravertebral joints" or lateral "facets". Now it appears that a great number of cases of backache, (secondary) spondylitis and sciatica are due to diseases primarily not in the larger, more obvious, vertebral bodies but in the smaller structures—disks and facets. Thus current writers have given much space to discussions on the "newer anatomy and pathology" of these tissues. Since the work to which they refer in truth constituted "a new chapter on vertebral pathology," it seems well to review it here in some detail. (Since current writers freely referred to the reports of Schmorl and the others just mentioned, it was at times difficult to know when they were quoting and when they were presenting original observations. The following is a summary of data reviewed by them—Ed.)

One is likely to consider the spine as consisting of 24 vertebral bodies with their 23 intervertebral joints. As a matter of fact, according to Rechtman³⁹⁵ there are 134 joints in the spine between the skull and the sacrum, each vertebra having approximately 10 synovial-lined cavities. Furthermore, the 23 intervertebral "joints"—the spaces between the vertebral bodies—are not true joints at all, since they possess no synovial membrane but are made up of fibrocartilage—the intervertebral disks. These disks are composed of three main parts: the cartilage end-plates, the annulus fibrosus, and the nucleus pulposus. Each disk is bounded above and below by a vertebral body, the peripheral bony edges of which are slightly thickened anteriorly and laterally (but not posteriorly) to form the "epiphyseal ring".

The cartilage plates are thin layers of hyaline cartilage which form the top and bottom of the intervertebral disk and which fuse anteriorly and laterally with the bony edges or epiphyseal ring of the vertebrae to form the "rim ledge". The cartilage plates in turn enclose the "annulus lamellosus" or "annulus fibrosus," a dense fibrocartilaginous envelope composed of concentric folds of fibrous tissue. These folds form a strong elastic container for the nucleus pulposus, except toward the posterior edge of the disk (toward the spinal canal) where the fibers of the annulus are fewer and thinner.

The "heart" or "central lens" of the intervertebral disk is the nucleus pulposus, a fibroglutinous incompressible mass of tissue, partly cellular, partly fluid (88 per cent water at birth). Thus it is subject to the usual laws of fluids—it is under tension, and is capable of expansion but not of compression. The pressure of the nucleus pulposus after cutting away the annulus fibrosus is 18 mm of mercury. The pressure required to reduce its expansion is 32.2 pounds⁴⁰⁰. The position of the nucleus pulposus within the annulus fibrosus varies in different spinal segments, it is always rather more posterior than central but is farther forward in the upper thoracic region. The nucleus acts as a shock-absorber and diminishes the effect of

stress and strain on the spine, and at the same time it is the medium of transmitting pressure from one vertebra to the next. It is confined to its normal shape and position by the strong surrounding bands of the annulus fibrosus and it is on the integrity of the latter and of the cartilage plates that the normal function of the nucleus depends.

The simplest way to understand the intervertebral disk is perhaps to regard it as a rudimentary (but not a true) joint, the cartilage plates are comparable to articular cartilage, the annulus fibrosus to fibrous articular capsule, and the nucleus pulposus to a joint cavity (Malcolmson⁴⁰¹). The disks have the function, then, of being buffers and hydrostatic ball-bearings (Hadley⁴⁰²), and it is largely on the integrity of these disks that the normal function of the spine depends (Carpenter⁴⁰³). The disks in embryonic life have blood vessels,⁴⁰⁰ but the adult disk is thought to have no blood vessels. It gets its nutrition by diffusion of lymph through minute perforations in the bony surface of the spongy vertebral bodies. The disk has no nerves either, and since it has no nerves, the disk when diseased is *per se* painless. Pain is produced only when secondary changes occur in vertebral bodies and facets (Hart⁴⁰⁴). Since the disks have no blood supply they cannot become infected directly through the blood stream, however, they may be infected via lymph channels, and suppuration in the region of a disk may attack and destroy it^{405, 406}.

The only true joints of the spine are those which connect the superior and inferior (lateral) spinous processes. In the literature they are variously named "lateral intervertebral articulations" or joints,⁴⁰⁷ "intervertebral synovial joints,"⁴⁰⁸ "apophyseal articulations" or "posterior articulations of the spine,"⁴⁰² and "articular facets"⁴⁰⁹. They are true diarthrodial joints and possess joint cavities. Hyaline cartilage covers their surfaces, and they possess synovial membranes, articular capsules and articular ligaments. Hence they are subject to the same injuries and diseases that affect joints elsewhere.

The function of these joints is to permit motion in the spine and to act as stabilizers, but not to carry weight, which in a position of good posture they do not carry. Each joint permits only a fraction of an inch of motion, yet many of them together permit an appreciable amount. Leverage determines to a large degree the amount of force transmitted to the capsules of these joints, it being progressively less toward the head and progressively greater toward the sacrum, the greatest force being at the lumbosacral joint because the lateral intervertebral articulations are more or less in the sagittal plane, except at the lumbosacral joint where they are more obliquely situated. Therefore, at the lumbosacral joint an antero-posterior roentgenographic view does not show the joints in profile as it does in higher lumbar joints.

Ligaments and muscles usually prevent damage to the lateral intervertebral joints, even to those of the lumbosacral region, where the fifth lumbar body is normally inclined upon the first sacral at an angle of 40°. Here,

forward slipping is prevented by the inferior articular process of the fifth lumbar vertebra and by surrounding ligaments. The spinal nerves escape on each side by way of the spinal foramina, which vary in size as do the nerves. Unfortunately the smallest of the lumbar foramina is the fifth, through which the largest nerve trunk passes, and this has much to do with the great frequency of low-back pain involving the fifth nerve.¹⁰⁷

Pathologic Conditions Affecting the Intervertebral Disk, Results Thereof The parts of the intervertebral disks are so interdependent that disease of one part leads to disease of others. *Cartilage plates* may be affected variously. 1 Congenital defects, fissures or cracks, may weaken them and lead to prolapse of the nucleus pulposus. 2 Acute trauma may injure them and cause prompt escape of the nucleus pulposus. Roentgenograms will be negative for several months until thinning of the disks becomes apparent, until the nucleus, if it prolapsed into the spongiosum, becomes calcified, or until secondary osteo-arthritic changes become obvious. 3 Chronic trauma, particularly in the third and fourth decades of life, may injure the plate.⁴⁰³ Fibrillation from wear and tear in hard workers or in the aged, or even continued every day trauma, will cause minute cracks in the plates, with resultant dehydration, lessened resilience, thinning and destruction of the disk, excessive wear and tear on the margins of vertebral bodies, and subsequent osteo-arthritis (Schmorl). However, since Schmorl often found better preserved disks in the aged than in people of sedentary occupation, he concluded that the ordinary trauma of daily work plus individual constitutional factors, which vary greatly in different persons, plays a greater rôle than disease in producing degenerative changes in the disks. 4 Primary disease of cartilage plates is unknown or rare, but they may be secondarily invaded by diseases of the vertebral bodies, for example, tuberculosis and osteomyelitis.

The *nucleus pulposus* may be affected in several ways. 1 Retropulsion, or antepulsion, of the nucleus within the disk⁴⁰³ or prolapse of a nucleus into the spongiosum of an adjacent vertebral body may occur, chiefly from injuries producing tears in the annulus fibrosus, in cartilage plates, or both. Retropulsion of a nucleus into the spinal canal may occur and produce pain (with or without neurologic findings) and even paraplegia (Malcolmson,⁴⁰¹ Carpenter,⁴⁰³ Mixter and Ayer⁴¹⁰). Schmorl found some degrees of prolapse of nuclei in 38 per cent of 5,000 routine necropsies. If only a small portion of a nucleus is extruded, function of a disk may not be seriously impaired for a time, but dehydration and diminished function of a disk may later appear at an earlier age than otherwise. 2 Lateral shift of a nucleus to the convexity of the curve may occur, as in cases of sclerosis.⁴⁰¹ 3 Calcification of the nucleus may result from unknown causes, presumably from disturbances in calcium metabolism, trauma, senility, infection and so forth.⁴⁰³ Such deposits increase with age. They may appear in the nucleus or in the annulus, Ratheke (1932 cited by Joplin) found 6.5 per cent of

them in the nucleus, 71 per cent in the annulus. They appear in roentgenograms as branched shadows with several processes, projecting outward. They are generally in the central portion of the disk, but also in the periphery of the fibrous ring. 4 Dehydration occurs with advanced age. The water content of the nucleus at birth is 88 per cent, at 18 years 80 per cent, at 77 years 69 per cent. Thus progressive dehydration begins in the third and fourth decade⁴⁰⁰ and accompanies senility, but stress and strain hasten its development and it can be rapidly brought about by leakage of the nucleus from the several causes noted⁴⁰¹. 5 Infiltration of the nucleus by other tissue may occur, by bone or blood vessels, and especially by fibrous tissue replacement of old age or during health after trauma. 6 "Expansion" of nuclei sometimes occurs from release of pressure when adjacent vertebral bodies become softened from osteochondritis, osteitis fibrosa, senile osteoporosis, or neoplastic invasion. As a result of nuclear expansion, the disks appear spherical in roentgenograms, the vertebral bodies appear biconcave⁴⁰³. In extreme cases adjacent intervertebral disks may almost touch⁴⁰⁰, roentgenograms then show thick disks and thin biconcave vertebral bodies. Enlargement of disks in such cases was believed by Schmorl (1930) to be due to "expansion," by Moffett (1933) to result from compensatory hypertrophy.

Disturbances of *intervertebral disks* include (1) congenital absence of a disk,⁴⁰¹ (2) drying of tissue of the disk, (3) occurrence of fissures primarily in the disk, and (4) increased moisture in tissues of the disk, inducing gross fissure formation and ultimately destroying the disk. Infection of the disk via the blood stream presumably does not occur as the disk has no blood supply⁴⁰². (This is doubted by Bohmig⁴¹¹). However, suppuration adjacent to a disk may attack and destroy it. Changes in the disk become so frequent with advancing age that, after the middle of the sixth decade, it is almost impossible to find a spine in which all disks are normal⁴⁰⁵. Degeneration in the disk is characterized by a grinding up and drying out process with deposition of yellowish or brownish pigment of unknown composition. Large cavities are produced in the interior, but the outer periphery of the annulus fibrosus may remain intact⁴⁰⁰.

The eventual thinning and tendency to partial or complete destruction of the disks plays a large part in the production of several clinical syndromes: (1) hypertrophic (osteo-) arthritis of vertebral bodies and of facets, (2) radiculitis at various levels, (3) sciatica, (4) low back pain with or without sciatica, (5) occasional symptoms simulating those of cord tumor.

When Keyes and Compere (1933) punctured the annulus fibrosus of animals and allowed nuclear material to escape with prolapse of the nucleus into adjacent vertebral bodies, there ensued destruction of the disk, lipping of vertebrae, and osteo-arthritis. The same sequence of events occurs in man. Whenever thinning and destruction of disks occur, the vertebral bodies rub together, causing sclerosis, osteo-arthritis and lipping⁴⁰¹. As

noted, since disks contain no nerves, disease of disks is not painful per se until the development of vertebral or facet changes⁴⁰⁰. Some regard the vertebral osteophytes as evidence, not of arthritis, but of an attempt at stabilization, hence they prefer "spondylosis" to "spondylitis" (Beadle, 1931)

It is important from the medicolegal standpoint to realize that the radiologic diagnosis of disease of disks may have to be delayed several months after injury until secondary changes occur. Roentgenograms may not at once reveal all the damage from acute trauma, nuclear prolapse is not at once associated with visible roentgenographic changes. Conclusions must be drawn from the width of the intervertebral space and the condition of the borders of the adjacent vertebral bodies. Weakness of cartilage plates may be evidenced radiologically by the pressure of smooth excavations (unbuccination of disk material) into vertebral bodies (Malcolmson⁴⁰¹). When nuclear prolapse occurs, the first change is a fibrous tissue reaction. About a month later this is replaced by a rim of cartilage which becomes surrounded by a wall of sclerosed bone. The space becomes hollowed, and later (three or four months after injury), deposits of calcium in vertebral bodies become visible in roentgenograms. These Schmorl's knots⁴⁰¹ or nodules⁴⁰⁰ were previously thought to be enchondromas of the intervertebral disk (Mixer and Ayer⁴¹⁰).

Pathologic Conditions Affecting the Facets, Results Thereof The lateral intervertebral joints or "facets" may be affected (1) directly as the result of trauma, degeneration or disease, or (2) secondarily in connection with disease of the intervertebral disks and vertebral bodies. Occasionally a sudden forcible motion of the spine is too great or too quick for muscles to protect the capsule of the facet adequately. The capsule is strained, some of its fibers are ruptured, and local pain and muscle spasm are found, but roentgenograms do not show the synovitis of these joints or the swelling of its capsular ligaments⁴⁰⁷.

Rupture of a nucleus pulposus and narrowing of a disk will cause subluxation of the adjacent facet articulations. If enough fluid escapes so that the nucleus is destroyed, the disk thins and the vertebrae begin to settle, the axis of motion is shifted posteriorly to the articular facets, and the weight of the body is transferred to the lateral or anterior part of the vertebral bodies. Partial subluxation of articular facets and a diminution in the size of intervertebral foramina ensues (this is nicely shown in photographs by Hadley,⁴⁰² and in diagrams by Hart⁴⁰⁴). Local and referred pains are produced by tension on capsular ligaments, encroachment on the size of the lumen of the foramina, and impingement of the ends of the articular processes on the pedicle above and the lamina below (both of which are covered by periosteum). The over-riding and abnormal contact of the surfaces of the facets produce degeneration of cartilage, marginal hyperplasia and

exostoses which still further decrease the diameter of the foramen and lead to radiculitis^{402, 406}

Production of Low Backache and Secondary Sciatica When the series of events just noted occurs at the lumbosacral joint it is particularly productive of symptoms, commonly low backache and sciatica. The sciatic nerve is derived from the anterior divisions of the fourth and fifth lumbar and the first, second and third sacral nerves. The fifth lumbar nerve is, as has been said, the largest one but must traverse the smallest foramen. It lies between the lumbosacral intervertebral disk and the lumbosacral articular facets and may become involved in inflammation, either of the disk or facets. Sciatic radiculitis frequently results.

That the intervertebral foramina are "the crossroads of neuralgia" was borne out by the experience of Putti⁴¹² who noted "vertebral sciatica" in 231 of 345 cases of lumbar arthritis. According to Ghormley (1933) sciatica is more frequently caused by pressure on nerves or nerve sheaths at diseased facets than by disease of intervertebral disks.

Lumbosacral congenital anomalies, present in about 35 per cent of all persons⁴⁰¹ are frequent, some say the most frequent cause of sciatica or low back pain (O'Conner,⁴¹³ Bellerose⁴¹⁴). The fifth lumbar vertebra is in the process of developmental transition. In Wagner's⁴¹⁵ cases defects here produced pain involving or including the third lumbar to the third sacral segment, but most particularly the fifth lumbar and the first and second sacral segments of the spinal cord.

In occasional cases sciatica was found by Ayres⁴⁰⁶ and Mixter and Ayer⁴¹⁰ to be due to rupture of the intervertebral disk into the spinal canal. About 50 per cent of such ruptures implicate the fourth to fifth lumbar disks. 23 of their 34 cases, 42 of 81 collected cases. Usually fragments of both annulus and nucleus were present, hence "rupture of the disk" is a more correct term than "rupture of the nucleus". The herniated mass varied from 0.5 to 2 cm. in size. Trauma was the most frequent cause. Symptoms may not appear immediately thereafter. In lumbosacral herniation symptoms may be of sacro-iliac or low-back pain, of severe intermittent sciatica, or of caudal tumors. (Malcolmson⁴⁰¹ noted paraplegia in one case). Neurologic examination was sometimes negative. The protein content of spinal fluid was almost always increased (in 33 of 34 cases), even in spinal fluid from above the level of the hernia. Injections of lipiodol revealed partial subarachnoid block. Therefore, not even a tentative diagnosis of herniated disk should be made without finding increased protein in spinal fluid and a positive lipiodol test.

(Among a fairly large number of cases in which rupture of the disk into the spinal canal was proved at operation by neurosurgeons at The Mayo Clinic were several in which the protein content of the spinal fluid was normal. In only 20 per cent of the entire series was there roentgenographic evidence of thinning of intervertebral disks—Ed.)

Of additional interest are the following representative articles on low-back pain "commonly caused" by a tight iliotibial band ^{389, 416} and a description of the Ober method of treating the condition by sectioning the fascia lata, arguments for ⁴¹⁷ and against ⁴¹⁸ the idea that backache is frequently caused by sacro-iliac subluxation, backache from the urologic viewpoint ^{419, 420}, gynecologic conditions, such as displaced uterus or malfunctioning ovaries as a common ^{421, 422} or rare ^{397, 398} cause of backache, the diagnosis of destructive spinal lesions by "needle-biopsy" ⁴²³, and on manipulation in low-back pain from trauma and poor posture (Cox, ⁴²⁴ Wright ⁴¹⁷) A partial translation of Cotugno's *De ischia de nervosa commentarius* (1764) was given by Viets ⁴²⁵ with interesting historical comments

The Treatment of Low-Back Pain and Secondary Sciatica This is most variable and depends on the cause Hart ⁴⁰¹ and Hadley ⁴⁰² favored conservative treatment physiologic rest (on a firm bed, with or without extension, strapping, jackets, braces) and hyperemia by various physical means Roentgen therapy was distinctly helpful, Hadley stated When conservative therapy failed, spine fusion or facetectomy was advised Of 99 patients with "lumbosacral pathology" seen by Ayres, ⁴⁰⁶ 59 had thinned disks The results of Hibb's fusion operation, followed by the use of a jacket or brace, were successful in 80 cases, patients being well two to 10 years after operation Facetectomy was not necessary, and Ayres felt that if it were done with fusion the resultant mass of callus might involve the fifth lumbar nerve adversely

COMMON TYPES OF SPONDYLITIS

Excluding spondylitis due to frank trauma and specific infection, Kreuscher ³⁹¹ distinguished three types hypertrophic spondylitis, atrophic spondylitis, "which generally goes on to ankylosis," and nonspecific "infectious spondylitis," which is "often relieved by removal of infected foci" (The distinctions are not clarified further—Ed) Some regard spondylitis rhizomelique, or the Marie-Strumpell type, and the von Bechterew type as different diseases Spondylitis rhizomelique, spondylitis ankylopoietica, and the von Bechterew and Strumpell types are all regarded by Buckley ⁴²⁶ as the same disease, "ankylosing spondylitis," which, however, he considered distinct from, and not the spinal equivalent of, atrophic arthritis, because of the sharply-contrasting sex incidence and because, with ankylosing spondylitis, it is rare for more distal joints to be implicated Even when peripheral joints are affected therewith, "such cases may be distinguished from rheumatoid arthritis by the order of invasion, the spine and large joints preceding those of the extremities"

(The editors consider that some of these distinctions are relatively unimportant, that the von Bechterew and Strumpell types are probably varieties of atrophic spondylitis, and that the two great common types of spondylitis are atrophic spondylitis, the equivalent of atrophic arthritis elsewhere, and hypertrophic spondylitis, the spinal representative of hypertrophic arthritis as seen in peripheral joints—Ed)

Atrophic Spondylitis The relative incidence of atrophic spondylitis to atrophic arthritis was 1 13 in one series¹⁰³

Symptoms The usual symptoms were reviewed by several, for example by Buckley^{426, 427} who also summarized studies on the nervous manifestations of "vertebral rheumatism" Root pains and reflex changes may occur in both types of spondylitis In hypertrophic spondylitis, nerve symptoms are due to formation of exostoses, not from inflammatory exudates in atrophic spondylitis, however, they are rarely due to compression from exostoses or ossified ligaments but to inflammatory lesions of the epidural spaces or meninges Nerve pains are more frequent in the pre-ankylosing stage than when the spine is fixed, but girdle pains in the lower intercostal regions may be present after ankylosis has begun, probably from new bone deposits on the sides of the vertebral bodies In cases of brachial neuritis and minor nervous symptoms in arms, profile roentgenograms may reveal atrophy of the lower cervical vertebrae, with or without spondylitis, a point for further investigation⁴²⁷

Pathology This was described again bony ankylosis of vertebral bodies, not from osteophytes, but from calcification of vertebral ligaments, circumferential ossification of intervertebral disks, rarefaction and softening of vertebral bodies, and destruction and ankylosis of sacro-iliac joints⁴²⁶ (Also ankylosis of lateral intervertebral joints [facets], and costovertebral joints — Ed)

Roentgenograms These reveal a variable state, ossification being early in some cases, late in others Several noted early involvement of sacro-iliac joints (Buckley,⁴²⁶ Dawson¹⁰³), and Scott⁴²⁸ regarded it as of particular significance Of his 110 cases of "spondylitis adolescens," all showed bilateral infections of sacro-iliac joints with ankylosis According to him, sacro-iliac infection is long symptomless and generally starts several years prior to symptoms in the sacro-iliac joints themselves or in the back elsewhere Later, wandering pains about the shoulders, arms, ribs and legs may appear in all such cases roentgenograms of the (painless) sacro-iliac joints should be taken to detect the early stage of spondylitis—the sacro-iliac infection According to Scott, spinal symptoms do not begin until ankylosis of sacro-iliac joints has begun

Laboratory Data The plasma fibrinogen and total protein were higher in 12 cases of atrophic spondylitis than in cases of atrophic or hypertrophic arthritis (in other joints) seen by Aldred-Brown and Monroe²⁵⁷ Agglutinins to hemolytic streptococci are present in much lower amounts than in atrophic arthritis elsewhere (Dawson¹⁰³)

Etiology and Pathogenesis The cause of the disease is believed by the majority to be the same as that of atrophic arthritis (elsewhere) Buckley⁴²⁶ was in sympathy with Leri's idea that atrophic spondylitis is not a disease of joints primarily, but of bone, "an infectious or toxic osteopathy," and that the bacterium might be found in spongiosa In seven of 13 cases he noted increases in phosphoric esterase (phosphatase) of the blood, but he

considered this insufficient proof of a primary bone disease. Scott⁴²⁸ believed the primary cause of spondylitis to be the early sacro-iliac infection, which "in spite of meager evidence" may commonly be of tuberculous nature. Because it is so important to prevent the spread of the infection to vertebrae, Scott stressed the necessity of discovering the sacro-iliac infection early, before spinal or even sacro-iliac symptoms have arisen, by making roentgenograms of the sacro-iliac joints in all cases with "wandering pains" in the back.

(Our experiences confirm the observation of Scott that sacro-iliac changes are often present long before other roentgenographic alterations. Buckley, however, did not note sacro-iliac changes in every case. Further investigation is necessary before one can accept the pathogenesis of the disease as outlined by Scott—Ed.)

Treatment Scott further noted that to remove the sacro-iliac focus, "trephining and curetting of the sacro-iliac joints before the onset of ankylosis are being tried," also, irradiation of the spine and sacro-iliac joints by low doses of roentgen-rays of medium wave length. No results were given. Conventional treatment was advocated by most removal of foci, physiotherapy, belts, corsets or braces, and manipulation in selected cases^{390, 398}. Mecholyt iontophoresis was of no value (Abel³²⁰). The use of vaccine gave no relief (Sherwood³⁰⁹), though it made supervision of patients easier. Wilson^{355, 356} noted relief with short wave therapy.

Hypertrophic Spondylitis The synonyms are spondylitis osteoarthritica, spondylosis, spondylarthritis. To illustrate the new anatomic distinctions, Hawley⁴⁰⁹ used the term "spondylitis" referring to changes in vertebral bodies, and "arthritis of the spine" referring to "true spinal arthritis"—that of facet articulations. Thus also Shore,^{408, 420} in his studies on osteo-arthritis of the spine, preferred the term "polyspondylitis marginalis osteophytica" for (hypertrophic) osteo-arthritis of the vertebral bodies, anatomically a different disease from "osteo-arthritis of the dorsal intervertebral joints, the small synovial joints of the vertebral column."

Symptoms Current reports stress the nervous symptoms that may arise. Rosenberger⁴³⁰ attributed some cases of Horner's syndrome to (hypertrophic?) arthritis of the last cervical and first thoracic vertebrae. On certain movements of the head some patients noted neuralgic pains referable to the precordium or scapula, or spasm of the trapezius muscle. When symptoms arise from involvement of the upper three cervical vertebrae, occipital or suboccipital headache and pains in the neck may arise³⁸². Keefer³⁸² considered sensory changes common, but according to Rosenberger they are uncommon, as the involved nerves carry no sensory fibers to the skin. Each of three sisters, aged 67, 51 and 45 years, presented to Zabriskie, Hare and Masselink⁴³¹ a curiously similar syndrome of hypertrophic arthritis of the last four cervical (in the oldest patient, also of the thoracic and lumbar) vertebrae, subjective numbness and tingling of finger tips and atrophy of the thenar muscles of both hands. The atrophy was

believed due to direct pressure on spinal nerve roots at some point of their exit from the spinal canal. The onset of symptoms in these cases was between 44 and 49 years of age. No parallel syndrome was found in the literature. However, atrophy of thenar and hypothenar eminences was listed in Buckley's⁴²⁷ review of nerve manifestations of vertebral rheumatism, also noted were atrophy of other small muscles of the hand, atrophy of the Aran-Duchenne type, root atrophy of muscles (especially of leg and thigh), paresthesias, numbness and slight anesthesia, and sometimes muscle fibrillation and reflex changes. It was noted that osteophytes are sometimes seen at the vertebral level of root pain but on the side opposite the distribution of pain, indicating that it is not the formed osteophytes that produce pressure on nerve roots, but those in course of formation—ones as yet unossified and hence not visible in radiograms. (Bisgard, 1932, also described neurologic symptoms common in cervical arthritis—Ed.)

Pathology Hypertrophic spondylitis increases with advancing age³⁸². Certain vertebrae are affected much more frequently than others. In his study of 126 vertebral columns with osteo-arthritis Shore⁴²⁹ noted no involvement between the first and second cervical vertebral bodies, and very infrequent involvement between the eighth cervical and fourth thoracic levels. There were three marked "outcrops"—regions of most frequent osteophyte production: (1) the cervical outcrop, between the third and sixth (with peak between the fourth and fifth) cervical vertebrae, (2) the thoracic outcrop, increasing in frequency from the fourth to the ninth and tenth thoracic vertebrae, osteophytes then receding in frequency between the tenth thoracic and first lumbar vertebrae, and finally (3) the lumbar outcrop, most notable of all, with osteophytes most frequently between the third to fourth and fourth to fifth lumbar vertebrae. The three "minimum-points" were at the "anticlinal" vertebrae, which are supposedly balanced with a minimal tendency to slide or rotate and through which a plumbline would fall in the erect attitude of the body.

These curves of distribution of osteophytes from vertebral bodies were not quite the same as those found for osteo-arthritis of the small thoracic intervertebral joints⁴⁰⁸. In the latter, the four main outcrops were the cervical (whose peak was between the third and fourth cervical vertebrae, the cervico-thoracic peak at the cervico-thoracic joint), the thoracic (peak between the fourth and fifth thoracic vertebrae) and the lumbar (peak between the second and third lumbar vertebrae). Zones of minimal incidence were between the seventh, eighth and ninth thoracic and between the sixth and seventh cervical vertebrae.

Roentgenograms According to Scott⁴²⁸ sacro-iliac joints in "spondylitis osteo-arthritica" exhibit no pathologic changes roentgenographically, a sharp contrast to the constant changes in "spondylitis adolescens".

(This observation is at variance with general experience. Others, Zollner, 1930, Smith-Petersen, 1932—cited by Keefer,³⁸² noted anatomic changes in sacro-iliac joints increasing with age—Ed.) Several papers reproduced roentgenograms

of the pathologic changes in intervertebral disks which may lead to hypertrophic spondylitis ^{100, 101, 102, 110}

Etiology and Pathogenesis Varieties of trauma are considered the chief cause—occasionally acute trauma, more often chronic trauma of certain occupations, or of long-continued weight bearing resulting from man's erect posture ¹⁸² The distribution of osteophytes of the thoracic intervertebral joints was interpreted by Shore ^{108, 120} as follows: the cervical outcrop is probably due to weight bearing in the joints of the already dorsiflexed cervical vertebrae, the cervicothoracic outcrop results from the use of the upper limbs, by movements of dorsiflexion transferred from the limbs to the thoracic skeleton and by associated action of the erector spinae muscles, the thoracolumbar outcrop is the result of weight-bearing in the joints of the dorsiflexed lumbar column and absorption of the lower thoracic vertebrae into the lumbar curve as lordosis is established

Trauma alone, however, does not explain these changes satisfactorily, and trauma is but the last in a chain of circumstances which cause hypertrophic spondylitis. The series of events culminating in the excess trauma that stimulates osteophyte production is, as we have noted, now thought to include degeneration of intervertebral disks as the feature of primary pathologic importance

Treatment Accepting current ideas on pathogenesis it is difficult to see how removal of infected foci could help much, as it could not lessen trauma or restore the integrity of damaged tissue ¹⁰³ However, in spite of his conclusions on the general production of osteophytes by trauma, Shore believed some cases might be due to toxic or bacterial infection. In a case of severe "lumbago" with narrowed intervertebral disks and marginal osteophytes Shore isolated hemolytic colon bacilli (it is not stated from whence). Vaccine was prepared and given with "striking results." The patient was "cured" and subsequent roentgenograms showed that the intervertebral disks had recovered their proportions and osteophytes had "become static." (The case is mentioned without details—Ed.) Good posture must be adopted so that facets won't have to carry weight ¹⁰⁷ Heat, rest, massage, and supports were approved. When conservative therapy was inadequate, more radical therapy was advised: traction, casts, spine fusion or facetectomy. Operative and non-operative indications and methods were reviewed by Kreuscher ³⁹²

GOUT AND GOUTY ARTHRITIS

A reawakened interest in gout is apparent. For 15 years only about three articles on gout have appeared annually in medical literature written in English. Last year, however, there were eight or more. The writers insisted that gout is not uncommon. The experience of their patients indicated that nowadays a case of gouty arthritis is much more likely to be called "rheumatic fever," "infectious arthritis" or "acute arthritis" than to be diagnosed correctly. Gout is seen with increasing frequency by those

on the alert for it. In England, three of every 1,000 insured workers become disabled thereby (Glover, 1924). Of workers at "hot occupations," (e.g. stokers) admitted to Buckley's clinic for rheumatism, 8 per cent had gout. He suggested that excess loss of perspiration altered the saline content of tissues and the solubility of sodium bi-urate.

Clinical features of classic gouty arthritis were reviewed by Gupta,⁴³² Cohen,⁴³³ Fitz,²⁶⁵ Hench,^{49, 106} Lockie and Hubbard,⁴¹¹ Monroe,⁴³⁵ Talbott, Jacobson and Oberg,¹³⁶ Volini and O'Brien.⁴³⁷ Among features stressed were these. Gout may affect the poor, the vegetarians and teetotalers as well as the rich, the meat eaters and the alcoholics.^{432, 431} Gout rarely affects females. 98 per cent of patients are males.^{49, 106} However, four women with gout were noted by Monroe and by Talbott et al. The age at onset of gouty arthritis is generally after 40 years, however, in 28 per cent of Monroe's cases it was under 30 years. The onset was at the age of 10 years in one of his cases and at 12 or earlier in the case of another.⁴³⁶ The first attack is likely to be in a large toe (in 74 per cent of one group⁴³⁵) but often a knee, ankle or other joint is affected and the great toe may long be spared. When the great toe is affected maximal tenderness is generally at its mesial surface.¹⁰⁶ A later, or even the first, attack may be polyarticular, with some tendency to migration. In spite of much pain and localized redness, attacks are often without fever or leukocytosis. Spine, hips and jaws which are rarely affected, were involved in some cases.^{435, 436} Since olecranon bursitis occurs at least five times oftener in gout than in atrophic arthritis, its presence should suggest gout.^{106, 437} The blood uric acid almost always becomes elevated, although not in some cases until late in the disease. It is occasionally normal even in a patient with tophi (Monroe⁴³⁵). It often returns to normal under adequate treatment but may remain elevated even though gouty arthritis is controlled (Cohen⁴³³). At a given time tophi are found in only 50 to 69 per cent of cases.^{106, 435} They are easily and repeatedly overlooked until sought by one suspecting gout. A "tophus" is not a tophus no matter where it is located until it is opened and found to contain urates. Roentgenograms are generally of little value in early diagnosis, generally become "characteristic" only late in the disease. Attacks of acute gouty arthritis subside "rapidly or grudgingly."⁴³⁵ Between early attacks complete functional restitution of joints practically always occurs. However, a few (12 per cent) of Monroe's patients were not entirely free of pain between acute exacerbations. When the acute attack is over, chronic symptomless gout still persists and must be treated.^{49, 106, 437} "Proven gout" from the pathologic standpoint means tophaceous gout, but a diagnosis of "presumptive gout" (provable from the clinical standpoint) must be entertained in all patients without tophi who exhibit the characteristic pattern of gouty arthritis—early acute attacks (in one or more joints, with or without hyperuricemia) with complete remissions, later, of chronic gouty arthritis.^{49, 106}

(Monroe's case 4, that of a male, is of special interest. The first attack at the age of 32 years involved hips and then knees, feet and many other joints including the jaws. After four months, recovery was "fairly complete." The diagnosis was rheumatic fever. Subsequently less severe attacks repeatedly involved practically all joints including the spine. Physical examination, at the age of 57, revealed tophi, hyperuricemia, swollen temporomandibular joints, fingers and ankles, and stiffened wrists, elbows, hips and knees. Roentgenograms of hands and feet showed "marked hypertrophic changes." In the absence of rheumatic carditis and with tophi ultimately present, Monroe concluded the first attack was also probably gout. Four months is very long for an initial arthritis of gout or of rheumatic fever. If all of this patient's attacks were of gouty arthritis, the involvement of jaws, hips, and spine makes it worthy of special note as we are unaware of any proved cases of gout in these joints in the literature of the past many years—Ed.)

The report of Gupta is also of special interest. He had records of 250 cases of gout and noted "the existence of 700 to 800 untreated cases of gout" in Nepal, India, which has a population of 40,000 to 50,000—an admittedly astonishing incidence of 60 to 70 cases of gout per 1,000 population. This was all the more unusual since great numbers of the natives, including many with gout, were absolute vegetarians and teetotalers because of great poverty or their religion. Six cases were detailed.

(Comment thereon is in order. Four of the six patients reputedly had "tophi," the authenticity of which would have been unquestioned had photographs of them or their contents been shown. It was not specifically stated that they were opened and examined. However, we are inclined to accept them as tophi since a characteristic history of gout was present in three of the four cases. One patient had "chalky concretions on ears and eyelids," and an eight-year-old boy who had had repeated acute podagra and "whose family had gout" presented tophi on ears and in nasal cartilages. Tophi on eyelids and in the nose have been reported, but they are most uncommon even in severe, chronic gout. Therefore, without more data one is skeptical. Patient 2 had acute attacks in great toes and knees with sciatica, his "mother, two brothers and a sister were gouty." Case 3 was that of a man without arthritis, whose radial neuralgia was considered gouty because of hyperuricemia and because atophan gave prompt relief after morphine and other drugs failed. Case 4 concerned a woman with a blood uric acid of 4.5 mg per 100 c c, "tophi," and a history of pain in her great toes. She had hypertension, interstitial nephritis and a recurrent bleeding tonsillar abrasion. A diagnosis of retrocedent gout was made since the "usual measures for gout" reduced blood pressure and stopped hemorrhages. The patient may have had gouty arthritis, but the diagnosis of retrocedent gout is debatable—Ed.)

Bassler⁴³⁸ reported gastrointestinal symptoms in 23 cases with "chronic and irregular forms" of gout. The symptoms were believed due to or associated with gout and included pyrosis, eructations, flatulence, constipation, heaviness and drowsiness after meals, abdominal and pelvic pain, colonic distress, colics and cramps, excess mucus in stools, nausea and anorexia. From these alone the diagnosis of gout cannot be made, it must be made on the condition of joints and the blood uric acid. "In gout the total uric acid per 100 c c of blood and urine combined is always above high normal.

Studies were made on 10 patients as to the uric acid and urea ratio using

1 to 55 as the standard and also on the alkalinity of the blood " (No figures or results are given to explain these statements—Ed) "The suggestion of the disorder comes from deposits of urates causing stiffness in the ligaments and are noticed (sic) in the feet and slightly less so in the hands" Bassler gave colonic instillations of oxygen for the intestinal toxemia of a "distinctly gouty woman" Within two weeks she was relieved of "night leg cramps, stiffness of knees and fingers improved markedly and she could flex the tips of her fingers to the palms for the first time in four years" Thereafter he treated with oxygen 22 cases of what he considered digestive manifestations of gout "In all but five cases a strikingly quick result on the symptoms took place"

(No data of any sort are given concerning the history, sex, physical examinations, blood uric acid concentrations, presence of tophi, roentgenograms of joints or laboratory tests on intestines It is impossible for us to conclude from the data given how many, if any, of the cases were of gout, and that the intestinal symptoms were relative thereto In the case of the woman just mentioned, no proof is given that she had gouty arthritis and not chronic non-gouty arthritis No figures are given to support the statement that oxygen instillations reduced the uric acid content of blood and urine—Ed)

One of Monroe's ⁴³⁵ patients regarded an attack of diarrhea and malaise as a regular warning that gouty arthralgia was soon to follow Another of his patients on a regimen for gout got relief from gouty arthritis but not from persistent salivation and hawking, for which a diagnosis of 'gouty bronchitis' had been suggested The incidence of vascular disease was definitely higher in his gouty than in his other patients with atrophic or hypertrophic arthritis Although there was a basis for argument, Monroe concluded that "irregular gout" was a highly speculative affair, evidence for which was usually most inadequate Volini and O'Brien ⁴³⁷ also concluded that the dyspeptic symptoms which Lichtwitz (1934) and others regarded as precursors of acute gout "are so much more frequently associated with gastrointestinal and gall-bladder disorders that they seem of little value as a warning sign"

(As one writer said, only one in four patients with gout receives a correct diagnosis, but it is also true that in some quarters only about one in four patients who receive a diagnosis of gout actually has the disease Slocumb,⁹⁹ for example, found several European physicians making a diagnosis of gout in cases of Heberden's nodes, or of transitory, mild subdeltoid bursitis, or in certain cases of chronic arthritis with "gouty dyspepsia" without tophi, hyperuricemia, or history of recurrent acute attacks and remissions One distinguished physician with a wide knowledge of classical gout expressed his feeling that solitary chronic arthritis of the second or third metacarpophalangeal joints of women or men was practically always gout even without hyperuricemia, tophi, or recurrent acute attacks the only basis for the idea was admittedly his "clinical experience" It has been said that the accuracy of a physician's criteria for gout can be judged on the number of his patients who have tophi or are females If more than 50 to 70 per cent of his patients have tophi he is too exclusive and is probably omitting cases of bona fide (even if pretophaceous) gout

If less than 35 to 40 per cent have tophi or if more than 2 to 5 per cent are females he is too inclusive diagnosing gout where it does not exist. Because tophiaceous or even pretophiaceous gout in females is very rare, it should be noted that the father of Fitz' ²⁶ patient, also two brothers and a sister, had gout and "one of his daughters has a persistently elevated blood uric acid though she has never had true podagra." One of Gupta's six patients was a woman, and the mother, two brothers and sister of another patient were also "gouty." One of Bassler's patients was a "distinctly gouty woman." Only four of Monroe's 59 patients were females. One was reported as having a "degenerating tophus." Further investigation ²¹² led Monroe to conclude that the nodule was not a probable tophus, and that although the history was very suggestive of gout, the very low level of blood uric acid and the unsettled matter of the 'tophus' made the diagnosis uncertain. All of which leads us to conclude that it is not always easy to decide when "gout" is truly gout, that the diagnosis of gout in females must be made with extra caution, and that, when it is made, full details in support thereof should be given—Ed.)

Agents Which Provolve Gouty Arthritis It is of diagnostic importance to remember that acute gouty arthritis frequently appears with changes of seasons (spring and fall), after gastronomic or alcoholic celebrations, after fixed festivals such as birthdays, Thanksgiving, Christmas or the Passover, after acute or even trivial trauma such as a day's automobile driving and while patients are receiving certain types of treatment such as salyrgan or other strong diuretics for cardiac decompensation, liver extract for pernicious anemia, ergotamine tartrate (gynergen) for migraine or for the pruritus of icterus, and, very rarely, after insulin (Hench ^{49, 100}). Hench noted that gouty arthritis was frequently provoked by activities incident to a hunting or fishing trip (tight boots, rough walking, damp and excesses in meat and alcohol). As a result some of his patients "had to be carried home—game, gun and gout."

Leukemia and polycythemia are not infrequently complicated by acute gout, as was lead poisoning formerly. Krafka ⁴³⁰ noted that any (hemolytic or hematonic) condition which tends to stimulate the erythropoietic system may provoke acute gout. Lead is an active hemolytic agent and every low blood count is compensated for by an increased marrow activity. Hemorrhages, "bleeding," and liver extract are marked hematopoietic stimulants. Bone marrow is stimulated, and an increase in erythrocytes results. Endogenous uric acid rises from the destruction of the extruded nuclei of the normoblasts in the maturation of erythrocytes. Acute gout ensues.

In line with the observation of others that starvation or high fat diets induce marked increases in blood uric acid concentration, Lockie and Hubbard ⁴³⁴ found that the administration of a high-fat, low-carbohydrate diet (fat 250 to 350, carbohydrates 30 to 50, protein 50 gm) for five to seven days promptly provoked acute gouty arthritis in four cases but did not affect patients with non-gouty arthritis. In some cases blood uric acid rose markedly and the urinary uric acid content fell, but the symptoms provoked were not directly dependent on the altered blood uric acid. The induced attacks were promptly relieved by diets high in carbohydrates, low

in fat The provocative diet was therefore proposed as a diagnostic test and it was concluded that diets high in fat and low in carbohydrates should be avoided for patients with gout The wisdom of this advice was confirmed by Hench¹⁰⁶ who noted the development of acute gout in several patients whose bacilluria was being treated by the ketogenic diet

(The diets of Lockie and Hubbard were not ketogenic as it is almost impossible to produce ketosis with a carbohydrate intake of more than 15 to 20 gm It should be determined to what extent ketosis must be approached to provoke gout—Ed)

Within 12 to 120 hours after almost any surgical operation patients with quiescent (unsuspected) or active gout are prone to develop acute gouty arthritis Coburn and Pauli¹⁷⁸ noted that surgical operations occasionally provoked a recurrence of rheumatic fever Hench^{49 106} found, however that the great majority of about 50 cases of acute postoperative arthritis were ones of acute gouty arthritis and approved the axiom "In cases of acute postoperative arthritis (especially in males over 40 years of age) suspect gout" Clinical and chemical details of two such cases were given (The provocative effect of surgical operations in gout is in striking contrast to the temporary benefit that almost any surgical operation may provide for patients with atrophic arthritis—Ed)

Laboratory Data Two of Miller's²⁹¹ six patients had some degree of hepatic inefficiency as shown by levulose tolerance tests Blood proteins in three cases of gout were as follows albumin 4.0 to 4.4, average 4.2, globulin 2.2 to 3, average 2.5, total proteins 6.9 to 7.3, average 7.1 gm per 100 cc²⁸⁷ (In neither of these reports did it state whether tests were done during active gouty arthritis or quiescent gout—Ed) Roentgenograms in gout may not be characteristic and frequently simulate those in chronic non-gouty arthritis (Doub¹¹)

Pathology Galantha⁴⁴⁰ described a new technic for the preservation and microscopic demonstration of urates in gouty tissues The crystals therein were beautifully demonstrated (Formalin dissolves urates promptly and gouty tissues fixed therewith will show no crystals, merely crystal clefts Galantha's method uses absolute alcohol as a fixative—Ed)

Etiology and Pathogenesis It is now commonly believed that an excess of urates alone is not the cause of gout but merely an index of the metabolic disturbance that causes it As Ray³⁵¹ stated, the etiology of gout is very obscure and estimations of blood uric acid are of satisfaction only to those who still believe purine bodies are causes of gout Observations supporting the idea that gout may be a more widespread disturbance of bodily equilibrium than a dysfunction of uric acid metabolism were made by Talbott, Jacobson and Oberg⁴³⁶ who studied the electrolyte balance of two gouty patients In one case 50 attacks were studied in 22 months, in another seven attacks in nine weeks Changes in water and salt metabolism were as follows diuresis began before any clinical or subjective evidence of gout was manifest A negative sodium and chloride balance accompanied this diuresis and there was also an increased excretion of potassium, calcium, am-

monium, titratable acid, phosphate and urate. The previous observation of others that prior to an attack there is a decrease in urinary uric acid, was not confirmed.

(Statistical data presented deserve full consideration and may suggest new treatments. Those who have made metabolic studies, particularly on patients with gout who consider themselves "well" when the acute arthritis is over, will agree that the authors need make no apologies for having presented studies on only two cases, for the studies were very carefully made over long periods. Because of the continual shifts in electrolytes, the authors considered it doubtful whether a period of normal fluid and electrolyte balance of significant duration is ever observed in patients with gout. However in these two cases the frequency of attacks was so great [averaging an attack in one case every 13 days, in the other every nine days] that one might regard these patients as having, not acute recurrent gouty arthritis but chronic gouty arthritis with acute exacerbations. Studies should be made on patients with earlier, less active gout to see whether they demonstrate long periods with a normal equilibrium. The second patient was a woman. While the published report does not state that she had tophi, we are informed that she had numerous tophi and, a few days after thyroidectomy, severe, postoperative, acute gouty arthritis²¹²—Ed.)

Habitual use of alcohol was admitted by 62 per cent of Monroe's patients. That gout may affect vegetarians and abstainers from alcohol indicates that excesses of food and drink are probably only precipitating factors, not the cause of gout. The majority discount the factor of infection except as a provocative, but some (Gupta,⁴³² Willcox⁴⁴¹) favor the infectious theory. Llewellyn's theory that gout is an allergic manifestation to specific proteins was attractive to Nisse⁴⁴². "a focus of infection is likely to produce repeated attacks of gout by sensitizing a joint, already handicapped by a defective purin metabolism, to the effects of the bacterial antigen produced by the focus." A reverse sequence was suggested by Willcox⁴⁴¹. "in gout there is often some chronic infection which has sensitized the body and which has caused the uric acid metabolism to be disturbed."

Treatment The diet proposed for treatment by Lockie and Hubbard⁴³⁴ contained 350 to 400 gm of carbohydrate, 50 gm of protein, and no more than 50 gm of fat. Attacks of acute gout were relieved thereby. Pisanì⁴⁴³ independently noted the benefits of a high-carbohydrate intake in gout and administered glucose orally, rectally, or intravenously, depending on whether gout was active or quiescent. Joltrain⁴⁴⁴ gave his patients skin tests with purine and non-purine containing foods and interdicted all foods to which the patient's skin reacted, as well as many purine-containing foods. Diet in gout is a matter of quantity rather than quality, according to Watson⁴⁴⁵ who regarded the use of small amounts of presumably dangerous foods as harmless. The diet should be purine-free for three to four weeks after an attack, then it should be low in purine but high in non-purine containing proteins (milk, eggs, cheese)^{49, 106, 433, 437}. A common mistake is to stop treatment as unnecessary once the acute attack is over. Interval treatment is essential to prevent not only the otherwise almost inevitable return of

gouty arthritis, but to control the potentially fatal effects of gout on the cardiovascular and renal system. Therefore, such a diet should be continued indefinitely. For this reason also some advise the intermittent use of cinchophen (three consecutive days each week) long after the acute attack is over. Although the routine use of cinchophen provides some risk to the gouty patient, it is, according to Hench,^{49 106} a minor and justifiable risk which must be taken whenever gout cannot be controlled by diet alone (which is very often the case). The mathematical chances of gouty patients being seriously or even fatally affected with gouty nephritis, renal stones, apoplexy or coronary disease (the not uncommon complications of gout), although moderate, present a more real danger than the rather remote chance of a significant toxic effect from cinchophen. Cinchophen and neo-cinchophen were used by Volini and O'Brien but, when contraindicated, were avoided in favor of salicylates and glycine, the synergistic action of which reputedly increases urate excretion (Quick, 1933). Cinchophen was avoided by Cohen⁴³³ in favor of colchicine given in small doses every fourth week between attacks.

Acute postoperative gout can generally be prevented, according to Hench⁴⁹ by the following regimen: for five to six days before and after operation the patient is given a purine-free, high carbohydrate diet, a generous intake of fluid, $7\frac{1}{2}$ grams (0.48 gm.) of cinchophen, t.i.d., and enough sodium bicarbonate to alkalinize the urine constantly. If a patient with gout must have liver extract for an associated blood dyscrasia, the experience of Fitz'²⁹⁵ patient should be recalled. He took orally four ampules of Lilly's liver extract No. 343 daily for three months without precipitating acute gout. Tired of eating liver, he was given one intramuscular injection, which was followed immediately by the worst attack of gout he ever had. Fitz quoted Minot to the effect that such provocation is rare. Another gouty patient with anemia had recently taken intramuscular injections of liver extract for several months without the development of acute gout or increased hyperuricemia.

A review⁴⁸ of results of fever therapy included the following: Berris' (1933) patient with chronic gout of three years' duration, who was unrelied by various measures and was unable to walk for four months, obtained "complete relief" after six fever sessions, being able to walk without pain after the second session. Auclair was also credited with good results in the treatment of gout, but no details were given. Slot⁴² found gold valueless in gout. A mixture of goose-grease, pig-fat, sheep-tallow and pitch "alleviates the gout in anyone. This goose-fat is worth more than any treasure," according to an amusing verse translated by Brooke⁴⁴⁶ from a Seventeenth Century manuscript.

Cinchophen Poisoning This was not reported in cases of gout last year. However, four patients with other diseases developed it. A woman with atrophic arthritis had "subacute yellow atrophy" after taking 30 tablets of

oxyiodide in 25 days. A Talma-Morrison operation was done, at which time the condition of the liver was apparent, the patient recovered (Clarke and Settle⁴¹⁷). A young woman whose primary disease was unstated, died several weeks after developing jaundice, the result of taking 30 tablets of Cinsa-Vess (5 grains, 0.3 gm, cinchophen, 1/200 grain, 0.0003 gm, colchicine per tablet) (Peluse⁴¹⁸). A young woman with rheumatic fever died with acute yellow atrophy after taking 37½ grains (2.48 gm) of cinchophen in five days (Fraser⁴¹⁹). A man, aged 52 years, became jaundiced and died after taking for three months "a patent medicine containing cinchophen", at necropsy hepatic cirrhosis but no central necrosis was seen. Isolated from the patient's urine was normal coproporphyrin, increased in amount because of damaged excretory power of the liver. This is considered the first report of the isolation of a porphyrin from the urine of a patient suffering from jaundice or hepatic disease (Watson⁴²⁰). Cases of acute yellow atrophy, some fatal, due to the use of "M S T" (Martin's specialized treatment) began to accumulate, it and two other patent nostrums, Morton's No 1 and No 2 (containing cinchophen or neocinchophen) were barred from the U S mails⁴²⁰. Gastric and duodenal ulcers have previously been produced in dogs by administering cinchophen. Schwartz and Simonds⁴²¹ found cats very susceptible, guinea-pigs moderately resistant, and rabbits very resistant, to massive doses of cinchophen, four of six cats but none of the other animals developed gastric ulcers. The undoubted production in humans of gastric or duodenal ulcers by cinchophen has not been noted clinically or at necropsy.

The Uric-Acid Problem According to Beer⁴²² many (non-gouty) patients with highly acid urine develop symptoms of renal or ureteral colic with microscopic or gross hematuria from showers of uric-acid crystals, gravel or stones. Uric-acid gravel is a conglomeration of uric-acid crystals, the "stones" are rarely larger than "half the size of a pin-head". Passage of gravel produces the same symptoms as those occurring with the passage of sizeable calculi. Urate stones and gravel are invisible in roentgenograms. The similarity to calculus disease in the presence of "negative roentgenograms" has caused confusion and wrong diagnoses of nephralgia, sympathetic nerve disturbances of kidney or ureter, and stricture or kinks of the ureter. In Beer's cases uric acid in the blood was not increased. After a shower of gravel, one may see with a cystoscope minute calculi on the vesical floor or protruding from swollen, traumatized ureteral meatuses. Uric acid crystals redissolve in the bladder, gravel does not, after a shower of crystals, they can be seen in the bladder only rarely, but if a fresh specimen of urine is preserved three to four days in a sterile test-tube, the crystals become apparent as typical "brick-dust". Generally the treatment in such cases is reduction of protein, increase of vegetables, fruits and water in diet, and the use of alkalis. In three of Beer's cases colic, ureteral obstruction, anuria and severe constitutional symptoms developed, and were relieved only by cysto-

scopy and ureteral catheterization. In one case showers of crystals were actually seen shooting from a ureter.

(These patients presumably had neither gout nor the "gouty diathesis," but apropos of the tendency of acute gout to develop within the first six postoperative days, it is interesting to note that in Beer's first case colic, hematuria and ureteral obstruction occurred "about the fifth operative day" after appendectomy. One of us (P. S. H.) has observed "ureteral flash-colics" without other urologic symptoms in a few cases of gout and has collected brick-red uric-acid gravel. This recalls the pamphlets of an earlier century "On the gravel and the gout"—Ed.)

Normal values for uric acid in the blood were redetermined with the revised micro-Folin method (1933) by Berglund and Frisk.⁴⁵³ The mean uric acid value for unlaked blood was 2.7 ± 0.07 mg per 100 cc for 89 normal women, 3.2 ± 0.08 mg for 43 normal men. These workers noted the effects of salyrgan, novatophan, euphyllin, caffeine, pituitrin and lithium urate on uric acid elimination in man. With normal or damaged kidneys they found a linear relationship between uric acid in blood and urine, the elimination index. Salyrgan increased uric acid excretion, not by altering the mode of urate elimination, but possibly by altering the state in which uric acid exists in blood. (Salyrgan influences plasma colloids—Ed.) The effect of novatophan was somewhat similar, there was no correlation between dosage and effect on uric acid elimination. Euphyllin also augmented uric acid excretion. Caffeine produced no significant changes in blood uric acid or glomerular filtration. The effect of pituitrin was difficult to interpret: there was halving of the elimination index but changes in blood uric acid and in the glomerular filtration rate seemed insignificant. In light of these experiments the authors discussed the rôle of glomeruli and tubules in the secretion of uric acid and presented data to show that the concentration of uric acid by the kidney can be greater than that of blood.

Quick⁴⁵⁴ found that after strenuous, but not after mild, exercise the excretion of uric acid, but not of creatinine, was markedly diminished, uric acid and lactic acid in the blood rose slightly but definitely. He concluded that the diminution of uric acid excretion was due to excess production of lactic acid. Since neither lactic acid nor strenuous exercise apparently affect renal function, the uric acid retention is somehow linked with the metabolism of lactic acid, with which liver is concerned. Hyperuricemia in eclampsia, chloroform poisoning, cardiac failure and pneumonia result from the increased blood lactic acid that occurs in these diseases. (This report suggests that patients with quiescent gout might provoke an attack by strenuous exercise—Ed.)

Cinchophen presumably mobilizes uric acid in human tissues and increases urinary uric acid 70 to 330 per cent. The administration of cinchophen generally causes (partial) evacuation of tissue-urates in about two to three days, after which additional doses do not augment uric acid excretion further. Furth and Edel⁴⁵⁵ attempted to discover whether the use of sufficient doses of phenyl cinchoninic drugs would completely evacuate rat's livers of their uric acid content. On the diet used the normal uric acid content of

rat's liver was rather constant, about 6.5 ± 1 mg per cent. On administering cinchophen and tolysin there was an equal and marked reduction, not a complete evacuation, of hepatic uric acid to an irreducible minimum of about 1.5 mg per cent. Although a maximal effect was obtained by about 0.01 gm of the drugs daily per kg of body weight, noticeable effects were obtained by 0.008 gm per kg daily (corresponding to a dose for man of only one-tenth of a single dose of 0.5 gm, $7\frac{1}{2}$ grains).

Although the excretory effect of cinchophen and tolysin was the same, the former was much more toxic to rats, as determined by a much greater loss of body weight.

(These experiments suggest that cinchophen and tolysin may be clinically effective in much smaller doses than now used—Ed.)

Of interest also are the studies of Matsuomoto⁴⁵⁶ regarding the effect of mechanical and chemical damage to kidneys on the excretion of uric acid by the liver (into bile) of rabbits. In general, there was an augmented, possibly compensatory, excretion of uric acid in bile.

In rats, Borsook and Jeffreys⁴⁵⁷ found that purines are converted into uric acid chiefly by liver and intestinal mucosa. Both these tissues actively convert guanine, xanthine and hypoxanthine. Mucosa alone converts adenine to any extent. Kidney and spleen have only a moderate, and striated muscle very little, effect on these purines.

PSORIATIC ARTHRITIS ARTHROPATHIA PSORIATICA

Two views exist regarding psoriatic arthritis: that it is a special entity, or that it is ordinary atrophic arthritis in a person who also happens to have psoriasis. Psoriasis may of course occur quite independently of a coexisting affection of joints and be only casually associated with any kind of arthritis. Thus it is not uncommon to see patients with atrophic or hypertrophic arthritis, or even rheumatic fever, with an entirely unrelated psoriasis. Because these incidental associations have erroneously been described by some as psoriatic arthritis, the existence of a true syndrome of psoriatic arthritis has been vigorously denied by many and the issue clouded. Certain features of psoriatic arthritis are quite distinct, one feature is practically pathognomonic according to Hench¹⁰⁶. Except in one anatomic situation, the appearance of psoriatic arthritis is quite like that of mild or moderately-advanced, only occasionally severe, atrophic arthritis, and is indistinguishable from it objectively or roentgenographically. In one regard, at least, psoriatic arthritis is rather unique. It may involve knees, ankles, feet, elbows, wrists and hands, but it has a special tendency to involve the terminal joints of fingers and toes, with or without involvement of other joints of fingers and toes. Furthermore, the nails adjacent to affected, terminal phalangeal joints of fingers and toes practically always exhibit definite psoriatic changes. These differentiating points are illustrated in photographs (Hench¹⁰⁶). Terminal joints of fingers and toes are

rarely involved in atrophic arthritis, as a rule only in the most severe cases and then only late. Terminal joints of fingers in hypertrophic arthritis are of course commonly affected with Heberden's nodes, but the terminal joints of toes are strangely exempt. Of diagnostic value, then, is the distinction that, in psoriatic arthritis, terminal joints of fingers and toes are commonly involved early in the disease, with psoriasis of adjacent nails. When these joints are not (yet) involved, psoriatic arthritis in other joints must be diagnosed by other features.

Psoriatic arthritis rarely comes with the first or with a mild bout of psoriasis. It usually attends a later or severe bout, when the patient has become careless in treating the skin lesion. In early phases of mild psoriatic arthritis a parallelism exists to some extent between the lesions of skin and those of the joints—when the skin is worse, arthritis appears, when the skin clears up spontaneously or under treatment, arthritis may diminish or disappear, even when the skin alone is treated. In severe or recurrent psoriatic arthritis articular symptoms may persist, the arthritis adopts its own rhythm and may be only partly relieved by measures for the skin.

Boots³¹ did not recognize psoriatic arthritis as an entity, it is not included in his classification and he stated: “(in rheumatoid arthritis) psoriasis is not uncommon and has been referred to as psoriasis arthropathica.” His colleague, Dawson,¹⁰³ took a more equivocal stand. Although he did not classify it or separate it definitely he stated, “the association of psoriasis in rheumatoid arthritis cannot be regarded as a mere coincidence.”

(In the early stages of psoriatic arthritis, joints may sometimes recover function and the articular disease become inactive to a degree and with a speed not expected in atrophic arthritis. Boots and Dawson both showed photographs of the same young girl. Boots labelled it “Rheumatoid arthritis in a child [Still's disease]. Note fusiform fingers and psoriasis.” Dawson labelled it “Psoriasis arthropathica.” The condition of the terminal joints is not well seen in the photographs, so that the reader cannot venture an opinion on which form she may have had, but it may have been psoriatic arthritis as it is noted that she recovered to an unusual extent—Ed.)

The main treatment for psoriatic arthritis is control of the psoriasis, with such additional routine measures for joints as are necessary. Hench favored Goeckerman's (1925, 1931) treatment of the skin: applications of White's crude coal-tar ointment and ultraviolet (quartz) irradiation.

Several general articles are noted, though they did not mention psoriatic arthritis: one on psoriasis as a possible allergic manifestation,⁴⁷⁸ and a review of the modern treatment of psoriasis.⁴⁵⁹ Sperry⁴⁶⁰ used large doses of theelin intramuscularly in repeated courses to control but not cure severe psoriasis. Elson⁴⁶¹ considered psoriasis an enzyme deficiency disease: “Massive doses of pancreas extract will cure psoriasis.” Two of Schwartz' patients⁴⁶² were benefited by the intramuscular use of colloidal manganese. According to Thurmon⁴⁶³ “the more severe or extensive the psoriasis the more gratifying is the result obtained with intravenous organic sulphur.”

HEMOPHILIC ARTHRITIS

Hemophilic arthritis may occur with each of three types of hemophilia (1) true hereditary hemophilia, in which the bleeding tendency is a recessive sex-linked characteristic appearing only in males and transmitted only by females, (2) hereditary pseudohemophilia, in which the bleeding tendency is a dominant sex-linked characteristic and an affected mother or father may beget affected children of either sex and (3) sporadic or spontaneous hemophilia, cases of apparently true hemophilia in which no hereditary bleeding tendency can be proved. Three patients with hereditary pseudohemophilia, two sisters and the son of one, all with recurrent hemarthrosis, were seen by Handley and Nussbrecher.⁴⁶⁴ Family records, clinical and laboratory data, and the genetic relationship of the disease to true hemophilia were discussed. With the knowledge that true hemophilia has never been proved to exist in females, diagnoses were made as given, but the possibility was considered that these sisters might have had true hemophilia, the first homozygous hemophilic females recorded.

Two cases of sporadic hemophilia with arthritis affecting boys were reported by Marr and Herrmann.⁴⁶⁵ The brother of one had died of hemorrhage, but no other evidence of hemophilia was found in either family. Congenital syphilis has been considered the cause of sporadic hemophilia, one of these patients had it, the other did not. Theories on etiology were reviewed.

The roentgenographic characteristics of hemophilic arthritis were summarized by Buus,⁴⁶⁶ and were as reported in previous reviews^{1, 2}. A feature "not described before" was "characteristic sharp angulations in the joint-surface, which later developed into an abrupt rectangular break in the surface, so that part of the latter sinks to a lower level."

The pathology of articular tissues was summarized by Buus, and that of hemopoietic (but not articular) tissues in three fatal cases was described by Custer and Krumbhaar.⁴⁶⁷

Treatment Of supreme importance is the control of hemorrhage. Blood transfusions were considered by some the most effective treatment.⁴⁶⁴ Vine's horse-serum treatment was helpful in one case,⁴⁶⁴ produced a severe reaction in another.⁴⁶⁷ Marr and Herrmann⁴⁶⁵ used several agents in two cases of recurrent hemorrhages. Best results were obtained by intramuscular injections of the patient's own blood. Blood transfusions were helpful, but intramuscular injections of the patient's or another's blood avoided the necessity of blood-typing. Good results were noted with protein sensitization by subcutaneous injections of sheep serum, by intramuscular injections of whole ovarian extract, or of blood from women at the beginning of menses or when pregnant. However, intramuscular injections of normal male blood were equally helpful; therefore, results did not depend on a high thrombin content of blood. Thus Birch's theory that hemophilia results from inadequate female sex hormones was considered unproved by these workers.

and others^{468, 469} Chew and his associates⁴⁷⁰ studied for about a year two hemophilic patients, first untreated, then treated with estrogenic substances by mouth and subcutaneously, corpus luteum hormone intramuscularly, and the gonad-stimulating hormone from urine of pregnant women subcutaneously. The use of these hormones did not alter the coagulation time or benefit the clinical condition. No relationship existed between blood coagulation and the amounts of urinary estrogenic substances recovered. There was more of the latter in urine from untreated hemophiles than from normal males. At times, the coagulation time of patients was greater with treatment than otherwise.

McFarlane⁴⁷¹ and Barnett⁴⁷² reported further experience with Russel's viper venom which they considered (1934) the most effective local hemostatic available. The venom possesses remarkable potency as a coagulant in "almost fantastic dilutions." In a dilution of 1:1,000,000,000 it will coagulate hemophilic blood in six minutes. The venom is used in a dilution of 1:10,000 in physiologic saline solution and is non-toxic and non-irritating. Wounds should be carefully cleaned and dressings soaked with venom solution applied, these should be kept in place and then left alone as much as possible. Alveolectomy, tonsillectomy, prostatectomy were done safely by this means. Peck, Crimmins and Erf⁴⁷³ regarded the venom of *Bothrops atrox* (Fer-de-lance) cheaper, more available and more effective than Russel's viper venom. Optimal dilution of the former was 1:10,000. Moccasin venom and a tissue extract (rabbit's lung) were ineffective.

In prophylaxis, a high-protein diet, much gelatin, and raw liver, and a diet high in vitamin B, were used by Marr and Herrmann.⁴⁶⁵

ALLERGIC, METABOLIC AND ENDOCRINE ARTHRITIS

These three "diseases" are the current ghosts of rheumatology. Their names continue to be mentioned here and there in the literature, but their form and substance are most changeable and wraith-like. One writer materializes them in the form of atrophic arthritis, in another reincarnation they may resemble hypertrophic arthritis or some other articular disease. Although heavily cloaked in conjecture and shrouded in uncertainty, they are quite respectable ghosts and sometimes appear in the best company, being approved of by scientists of standing. And it is quite possible that, in time, any one or all of them may be born with a registered name and material body, definite in their clinical picture, etiology and pathology. All the recognized arthritides have had to struggle through years of embryonic life before they were born and finally accepted.

"*Allergic Arthritis*" Almost every type of joint disease has been considered an allergic reaction. Some regard food, others bacteria as offending antigens. Some believe the arthritis is actually caused by allergic reactions. Others admit allergic manifestations are present but regard them as of secondary significance, symptoms and not the cause of the disease. Many

writers do not make the distinction clear but just discuss this or that type of arthritis as "allergic" The "allergic phases" of various arthritides were briefly noted by Brown²¹⁴ who reminded us of Turnbull's (1924) views on chronic arthritis from food allergy We have noted arguments for and against the (bacterial) allergic nature of rheumatic fever and atrophic arthritis Intermittent hydrops is regarded by many as an allergic arthritis from unknown (food or bacterial) antigens Serum sickness was again mentioned as the prime example of allergic arthritis (As a matter of fact most allergists do not consider it an "allergic" but an "anaphylactic" arthritis, an antigen-antibody reaction and not true allergy—Ed) Contributing no new data Brown argued that "in every case of arthritis" the likelihood of food or bacterial allergy should be considered and skin tests should be made with food and bacterial antigens Offending foods should be avoided and patients should be vaccinated against offending bacteria

(Most physicians do not accept suggestions such as these because of the notorious unreliability and difficulty of evaluating skin tests to food and bacteria, and because of the rarity of undoubted clinical examples of allergic arthritis in which the food or bacterial antigen was definitely identified by provocative and therapeutic tests—Ed)

Myers³⁹ suggested the following as a case of "allergic arthritis"

A 34 year old man had had attacks of pain, redness and swelling in one or both feet each fall for three years The first metatarsophalangeal joints and dorsum of the feet were chiefly involved Attacks came suddenly, lasted 5 to 10 days, and then subsided The present attack affected the right foot and great toe first, 6 days later the left foot and great toe Erythematous tender areas were noted particularly over the medial aspect of the left metatarsophalangeal joint and dorsum of the foot After two days on rest and salicylates the pain disappeared, swelling left three days later Because the patient had had recurrent asthma each winter for four years, hay fever each fall ("late August until late October") for two years and chronic sinusitis for several years, and was "skin-sensitive" to pollens of ragweed and goldenrod, Myers suggested that "the arthritic symptoms were a response to an allergin" (inferring a pollen?—Ed)

(Data are incomplete but suggest acute recurrent gouty, not "allergic," arthritis The seasonal incidence (each fall), rapid onset, involvement of great toes, erythematous tenderness at the mesial aspect of great-toe joints, the rapid full joint recovery, —all are compatible with gout Blood uric acid was not mentioned The right foot was attacked October 7, the left October 13 Had the patient's arthritis been related to pollen one might expect it to appear in August or September, not at the end of the hay-fever season Furthermore, arthritis antedated the asthma by three years and the hay fever by five Skin tests were done with pollens, not with bacteria from sinuses No provocative tests with presumably related allergens were done Had allergic arthritis been suspected, response to epinephrine might have been more immediate and instructive than to salicylates The problem of "allergic arthritis" would seem to be confused rather than clarified by such incomplete studies—Ed)

The question of "articular or periarticular hives" is raised by the case report of Dubbs⁴⁷⁴ An elderly woman with "mild recurring attacks of atrophic arthritis" and spindle deformity of finger joints developed "cold

allergy " in exposed skin, the short (5 to 10 minutes) attacks of which added other symptoms unrelated to her arthritis, such as wheals, tingling, itching, and redness, and swelling of the fingers, back and neck. These symptoms were abolished by administration of epinephrine. Dubbs considered the reaction essentially cutaneous and subcutaneous, not articular or just periarticular.

"Metabolic Arthritis" This term has never been satisfactorily defined. By it one writer means "atrophic," another "hypertrophic" arthritis. Still others mean "gout" or "articular pains with hypo- or hyperthyroidism." Under the broad definition of "metabolism" many if not every arthritis is a "metabolic" arthritis, but by a narrower definition it would be an arthritis due to some recognized abnormal metabolism of food. No definite consistent metabolic error has ever been identified with any of the arthritides except gout and alkaptonuria and, even here, the nature of the fault is very obscure. The year's literature added nothing to justify the term.

"Endocrine Arthritis" This term has been variously used also as a synonym for almost every type of arthritis. Particularly confusing is the term "menopause arthritis" which is applied by one writer to cases of atrophic, and in other instances to hypertrophic, arthritis appearing near the menopause. Others give it a special meaning—a villous synovitis of knees in women about the menopause, but definitive clinical and pathologic data are not at hand. Since most of the arthritides are general diseases, sometimes with extensive secondary physiologic disturbances, it is not surprising that disturbances in endocrine function are found, but no consistent etiologic relationship between any form of arthritis and any recognizable endocrine disturbance has been proved.

Robinson³⁴⁰ accepted Llewellyn's conception of "menopause arthritis"—villous synovitis in traumatized joints, especially knees, with hypothyroidism prior to the menopause. "It may come on several years before or round about the time of the cessation or several years afterwards" (The vague time relationship alone would seem to refute the appropriateness of the term—Ed.) Periarthritic fat pads give an appearance of joint enlargement, the cavity is distended with synovial proliferations or fluid. The joints creak and revealipping of bone in roentgenograms. Robinson (1926) reported cases affecting young women with amenorrhea which were relieved when menstruation was restored by intrapelvic diathermy, of which he again approves. To many the syndrome is identical with hypertrophic arthritis, but Gray²⁵¹ accepted it as a separate entity.

The relationships between chronic arthritis, hyperthyroidism, and myxedema were discussed by Monroe²⁹⁶. According to another²⁹⁵ atrophic and hypertrophic arthritis are badly mixed up with the endocrines.

Relation of Arthritis to Parathyroids, Parathyroidectomy for Arthritis Because he found hypercalcemia and decreased electromuscular excitability in some cases of "ankylosing polyarthritis and spondylarthritis," Oppel (1926) suggested that these diseases were due to hyperparathyroidism and

proposed parathyroidectomy therefor. The idea was advanced by certain French and Russian workers and by Ballin and Morse (1931) in this country, but it has been sharply denounced by many. Schkurov²⁰⁸ reported results of "parathyroidectomy" in 83 cases (or 86, both figures are given) of "chronic rheumatic polyarthrititis and spondylarthrititis." Values for blood calcium before operation ranged from 8 to 17 mg, after operation 7 to 15 mg per 100 cc. Blood calcium before and after operation, respectively, was below 9 mg in 6 and 16 per cent, between 9 and 10.9 mg in 52 and 55 per cent and 11 mg or above in 42 and 29 per cent. Thus there was a postoperative shift from high to normal and from normal to sub-normal values for calcium. Immediate results from the operation were noted "in all cases" less muscle and joint stiffness and pain, and increases of 10 to 55° in joint motion. The results six months to four years later were noted in 40 cases. They were "good" (subjective and objective improvement) in 55 per cent, "satisfactory" (subjective relief only) in 35 per cent. Four patients were unrelieved or were worse. Schkurov concluded that parathyroidectomy cannot affect existing ankylosis but prevents ankylosis and will "do away with rigidity of joints."

(Containing conflicting statements, poor arithmetic, shifting premises and conclusions impossible of acceptance, this report is open to sharp criticism. It is our opinion that if any significant relief was obtained it was not from parathyroidectomy or any associated alteration in calcium but was in all likelihood entirely non-specific—the temporary relief which may follow, sometimes dramatically, almost any surgical operation. Schkurov reported hypercalcemia in 42 per cent of his cases. The method is not stated and the figures seem questionable since many excellent investigators have failed to find hypercalcemia in arthritis, except in rare cases. No metabolic studies, data on blood phosphorus or phosphatase, or urinary calcium and phosphorus were reported. He says "An important objective effect of parathyroidectomy is the decrease of blood calcium." But 52 per cent of his patients had a normal blood calcium before operation and only 3 per cent more [55 per cent] had normal values after operation. Parathyroidectomy was done in cases with and without hypercalcemia, yet admittedly results were the same in each group. But because some who had normal blood calcium were benefited he then advocated surgery for patients with rigidity of joints or a "tendency to ankylosis" even if the calcium was normal.)

He stated subjective improvement was obtained "in all cases," but this would then include one case in which "the patient did not feel any improvement for an entire year, but afterward pain subsided and mobility of joints was increased." Although "all" patients obtained immediate improvement, results six months to four years thereafter were only "good" in 55 per cent, and if the following is a representative case this figure is also open to question. A young woman had "contractions of the hip, both knees, elbows and wrist joints. Before operation she walked in a squatting position with the help of legs and hands—almost creeping. After parathyroidectomy and subsequent treatment by extensions" there resulted "an almost complete correction of all deformities" and "full restoration of all movements of joints." It is difficult to believe this, or certainly to ascribe it to parathyroidectomy rather than to manipulations.

The statement most destructive to his proposition was that in 23 [or over a fourth] of the 83 cases "histologic examination [of tissue removed at operation] did not

show any evidence of parathyroid gland tissue," in spite of which several had subjective improvement and a lowered calcium. We cannot understand why he included them in a discussion on parathyroidectomy and statistical results therefrom. Obviously, results could not possibly be from parathyroidectomy [which wasn't even done in 28 per cent] or from the inconsistent shifts in blood calcium. In some cases edema of the feet completely disappeared after operation, but in at least one case it reappeared when the patient began to walk. This too suggests that results were non-specific from an operation, from bed rest, relief of trauma and of static edema—Ed.)

At first Schkurov suspected the results were due to suggestion, not to parathyroidectomy. He discarded this idea when autohemotherapy without parathyroidectomy gave no relief. Having also noted relief even when removed tissue contained no parathyroid tissue, Simon and Weil (1932) ascribed it to removal of thyroid tissue or of fat. This led them to make a simple skin incision without touching the parathyroids; results were also satisfactory. Bach²⁹⁷ and Rankin⁴⁷⁵ criticized Oppel's work, stating that no metabolic studies were done, that the diagnosis was made on single determinations of serum calcium, that at operation parathyroid tissue was not always removed or even identified, and that symptoms often recurred rapidly. The fact his results were as good whether parathyroid tissue was removed or not, Oppel considered was because operation produced parathyroid ischemia by interfering with the nerve and blood supply. According to Bach equally good results were obtained by Weill who merely exposed the glands, and by Simon who applied chemical irritants to the thyroid gland. Those who have performed parathyroidectomy have claimed that if the operation is successful, on the same evening or on the day after, pain and periarticular swelling are markedly diminished and movements which were formerly painful become painless.

(These same dramatic, but generally temporary, results have been reported after removal of teeth, tonsils, appendix, gall-bladder, spleen, sympathetic ganglions, and other tissues. Bach²⁹⁷ noted similar dramatic results after thyroidectomy—Ed.)

Authors with a large experience with undoubted hyperparathyroidism in this country (Bauer,⁴⁷⁶ Bauer and Camp,⁴⁷⁷ Lahey and Haggart,²⁷¹ Mason and Gunther,⁴⁷⁸ Rankin⁴⁷⁵) all agree that parathyroidectomy cannot be sanctioned for arthritis and that "ankylosing arthritis" is not from hyperparathyroidism. One cannot even justify exploring the parathyroid glands of patients with skeletal changes until one has obtained chemical or pathologic evidence that such changes are due to hyperactive parathyroid tissue. In a study of 200 patients with atrophic arthritis Lahey and Haggart found no evidence whatever of hyperparathyroidism. Serum calcium and phosphorus were consistently normal and roentgenograms never revealed features of hyperparathyroidism. In 100 cases of atrophic and hypertrophic arthritis Hartung and Greene²⁵⁸ found no evidence of hyperparathyroidism in 97 per cent the blood calcium was normal.

Although the two diseases are unrelated, the skeletal pains of hyperparathyroidism are sometimes diagnosed "rheumatism" or "arthritis." In

hyperparathyroidism the shafts of bones are involved in local and generalized softening, destruction and cyst formation. Current reports gave details of about 50 cases. In at least 14 symptoms included pains in legs, arms, thighs, and lower back, and sometimes in hands and feet. Some of these cases were frankly considered arthritic until the characteristic roentgenographic and chemical alterations of hyperparathyroidism were discovered. The latter are fully discussed in several good papers (Albright,¹⁷⁹ Bauer,⁴⁷⁰ Bauer and Camp,⁴⁷⁷ Borg,¹⁸⁰ Castleman and Malloiy,¹⁸¹ Cuthbertson and Mackey,⁴⁸² Lahey and Haggait,²⁷¹ Left, Blanchard and Peabody,⁴⁸³ Mason and Gunther,⁴⁷⁸ Quick et al,⁴⁸¹ Rankin,¹⁷⁵ Robbins,⁴⁸⁵ Taylor⁴⁸⁶)

MISCELLANEOUS TYPES OF JOINT DISEASE

Hemorrhagic Villous Synovitis due to Xanthoma Kling and Sashin⁴⁸⁷ reported one case. A knee was painful for two years. Hypercholesteremia (238 to 288 mg per 100 cc) was repeatedly present. Presumably a disturbance of lipid metabolism caused lipid precipitation and xanthoma formation. Synovectomy gave relief. Twenty cases previously reported were reviewed. Symptoms resemble those of inflammation or internal derangement. Preoperative diagnosis may be made by finding an increased bilirubin and cholesterol content in the effusion.

Synoviomias (Benign and Malignant) Tumors of articular structures other than bone are rare. Synoviomias apparently originate from capsule or synovial membrane of bursae or joints, usually a knee. Less than 100 synoviomias have been reported (Razemon and Bizard, 1931) of which 43 were benign, 29 malignant. They may grow slowly and be regarded as "synovitis" for years before being correctly diagnosed. Amputation is often necessary. Coley,⁴⁸⁸ Wagner⁴⁸⁹ and Adair⁴⁹⁰ reported several cases, and discussed their pathology and treatment. A malignant synovioma may invade bone, but it does not produce osteoid tissue although it has the objective characteristics of a bone tumor. Hodgson and Bishop⁴⁹¹ saw one affecting a man aged 28 years. His left knee was affected by a rapidly-growing tumor which soon metastasized to adjacent skin and lymphatics. Roentgen therapy and Coley's toxin were useless, the patient died in seven months.

Anomalous Synovial Cysts Black⁴⁹² found two such cysts during classroom dissection. One cyst, 18 by 15 by 10 mm, was on the dorsum of the hand of a young laborer, between the first and second left metacarpals, and was inconspicuous until superficial fascia was removed. It did not connect grossly with synovial membrane of joints or tendon sheaths. The other cyst (16 by 10 by 8 mm) formed an obvious swelling on the medial side of the fourth left phalanx proximal to the first interphalangeal articulation. It originated probably from a knife-stab.

Tenosynovitis This most often affects a wrist or the peroneal tendons in the leg. Splints on lower extremities are cumbersome. Fieldman⁴⁹³

recommended the use of Unna's Paste Boot such as is used for varicose veins. It produces the least limitation of motion.

Cysts of Fibrocartilages of Knee Joint Fifty cases reported to 1930 were reviewed by Taylor¹⁹⁴ who reported four more. Cyst formation in menisci are commoner (72 per cent) in men than in women (28 per cent), in external more often (82 per cent) than in internal cartilages (18 per cent). Trauma is the usual cause. Menisci become contused. A degenerative process in fibrocartilages results in multilocular cysts. Symptoms are localized pain, swelling and sometimes stiffness. Treatment is removal of the entire cartilage. Lesser procedures (removing or curetting cysts) are followed by recurrences.

Leukemia Resembling Rheumatic Fever Some children with leukemia have fever and migratory joint pains without visible inflammation or roentgenographic changes. Others have acute arthritis with inflammation, roentgenograms showing focal areas of bone absorption, periosteal elevation and other changes. When cardiac murmurs from anemia are present and enlargement of lymph nodes and spleen is absent, the condition often resembles rheumatic fever before the blood picture becomes definite. Diagnosis may be suspected from the lack of effect of salicylates, it is eventually made on the appearance of abnormal leukocytes in blood. Three new cases of lymphatic leukemia resembling rheumatic fever affecting children were recorded by Smith¹⁹⁷.

Keratoderma with Arthritis Hyperkeratosis of skin and nails with arthritis may occur in gonorrhea—keratoderma blenorrhagica. Patel⁴⁹⁵ saw an unusual case of keratoderma and arthritis affecting a Mohammedan boy without history, signs, or symptoms of gonorrhea. This boy, aged 9 years, noted painful swelling of several joints and painless nodules on his legs. Recurring fever, progressive cachexia and arthritis developed. Examination two years later revealed arthritic dislocation of the right knee and a wrist, flexion deformities of an elbow, both hips and left knee, huge rupia-like keratoid masses of growth on both legs—painless, hard to touch and brownish, and hypertrophy of nails. There was no evidence of syphilis. Interesting photographs were shown.

Mycotic Infections Meyer and Gall⁴⁹⁶ reviewed 60 reported cases of mycosis of the spine: 47 from actinomycosis, 12 from blastomycosis and one from sporotrichosis. Mycotic spondylitis is generally secondary to a primary respiratory or intestinal focus. Vertebrae are infected either by direct contact with a suppurating focus (in which case the external surfaces of vertebrae are eroded), or by vascular metastasis (in which case bone destruction is central and surrounded by a condensed ring of bone). Symptoms may be slight or marked. In these 60 cases a clinical diagnosis was made in only nine. Diagnosis is very difficult and not often made until late in the disease or until death. Mortality was 90 per cent.

In mycotic spondylitis involvement of intervertebral cartilages and the formation of osteophytes and periosteal inflammation are not generally seen.

The disease is generally mistaken for Pott's disease, from which it can be differentiated as follows: in mycosis the angular deformity typical of Pott's disease is most often absent because of the capsule of dense bone which surrounds the destroyed area and prevents flattening of vertebral bodies. Mycosis reveals multiple sinuses, more destructive invasion and a more rapid opening of abscesses than in Pott's disease. The skin lesions in mycosis are characteristic. Roentgenograms in mycosis show the following, none of which are often seen in Pott's disease: cortical erosion of vertebrae, also erosion of articular processes and pedicles, and cavity formation in the cancellous portion surrounded by a zone of increased density.

About 45 cases of *Torula* infection in man have been reported. Usually the nervous system, rarely the skeletal system, is involved. A young man seen by Kessel and Holtzworth¹⁹⁷ bruised a knee slightly. It became increasingly painful, swelling, effusion and flexion deformity ensuing. At arthrotomy *Torula* organisms were recovered, and animals inoculated therewith developed lesions. The patient developed *Torula* lesions of both breasts, but these responded to roentgen therapy. The granulomatous condition of the knee did not respond to treatment and amputation was necessary a year later.

Arthrokatachysis of Hip Joints Levinthal and Wolin⁴⁹⁸ reported five cases. This imposing name means "subsidence or sinking-in of a joint." It is not a specific disease but a feature which may occur "in osteo-arthritis, gout, gonorrhea, syphilis, tuberculosis, trauma or endocrine disturbances." It was previously called "osteo-arthritic protrusion or intrapelvic protrusion of the acetabulum (Otto pelvis)." The characteristic feature is protrusion of the acetabulum into the pelvis and a narrowed hip joint space. It results from weight bearing and muscle pressure at the diseased joint. The femoral head bores its way through a weakened acetabulum into the pelvis. Symptoms are those of progressive chronic arthritis. Roentgenograms are characteristic: deepened acetabulum, thinning of the medial and inferior wall, eburnation, and narrowed space. If conservative treatment (heat, massage, traction) fails, casts or braces, arthroplasty, or arthrodesis, are indicated.

"A Syndrome of Unknown Etiology" Christian⁴⁹⁹ summarized reports of two patients who had long continued fever with inflammation of serous and synovial membranes (pleurisy, pericarditis, arthritis) and who eventually died of glomerulonephritis. Numerous laboratory tests failed to elicit the causal infection. The two cases were previously described by Tremaine (1934) as "Subacute Pick's Disease (Polyserositis) with Polyarthritis and Glomerulonephritis." (Christian noted that some patients have skin lesions suggestive of lupus erythematosus. To us the cases seem to be of acute, lupus erythematosus disseminatus, one with and one without skin lesions.—Ed.)

Acute Postoperative Arthritis Some cases were identified by Coburn and Paul¹⁷⁸ as recurrences of rheumatic fever provoked by surgical operations. Of cases of acute postoperative arthritis seen by Hench^{49, 106} a few were of rheumatic fever but the great majority were gouty arthritis, clinically

proved by past histories, physical and laboratory signs of gout, and response to treatment

DISEASES OF MUSCLES, FIBROUS TISSUE AND BURSÆ

Introduction Classification A study of diseases of muscles is largely an excursion into the unknown⁵⁰⁰ Various classifications of such diseases are in vogue

Shelden⁵⁰⁰ classified them briefly into (1) conditions in which disease of muscles is incident to a general infection (for example, rheumatic fever), with convalescence muscles recover rapidly and no special attention is paid them, fortunately, the muscular system generally has a high degree of immunity to infections which affect other organs, hence muscles are but infrequently and transiently involved, (2) diseases peculiar to muscles themselves, which are rare but important and include acute and chronic (true) myositis, dermatomyositis, myasthenia gravis and the neuromyopathies Ornsteen⁵⁰¹ approved Batten's (1904) classification of inflammatory diseases of muscles (1) primary infections, (a) acute polymyositis, dermatomyositis, hemorrhagic myositis, polymyositis with erythema multiforme and urticaria, and pseudotrichinosis, (b) neuromyositis, (c) tuberculous myositis, (d) syphilitic myositis, and (e) myositis with trichiniasis, (2) secondary infection in the course of acute or chronic disease, (a) myositis with specific fevers (typhus, typhoid, smallpox), (b) infective myositis with pyemia, infective endocarditis, glanders, gonorrhea, puerperal infection, infected wounds, actinomycosis, erysipelas, etc., and (3) myositis with special terminal lesions, (a) myositis ossificans progressiva, (b) general or localized myositis fibrosa

(The necessity of using a classification 32 years old is evidence of lack of progress in this field This classification does not specifically mention the common form of "myositis," every-day muscular rheumatism (intramuscular fibrositis) In discussions of "Myositis" one must distinguish between (1) "true myositis," parenchymatous diseases of muscles where definite primary pathologic lesions of muscle cells are seen, and (2) interstitial muscle disease, in which primary lesions are almost if not entirely in supporting fibrous tissue and in which muscle cells are rarely ever involved in demonstrable disease except slightly and secondarily This form or forms, Gowers, Stockman and others have called "intramuscular fibrositis"—Ed)

FIBROSITIS

Fibrositis is an inflammation of connective tissue Common sites for fibrositis are in deep fascia, muscle sheaths, subcutaneous tissues and fibrous portion of joint capsules and related ligaments Classified on anatomic grounds the main forms are panniculitis (fibrositis of subcutaneous tissue), bursal or tenosynovial fibrositis, fascial and intramuscular fibrositis, periarticular fibrositis, and perineural fibrositis^{337, 388, 441} On etiologic grounds it is classified as infectious or toxic, and traumatic (Telling⁵⁰²) or as in-

inflammatory fibrositis (from infection, toxins, or trauma) and degenerative fibrositis (from tissue age) (Buckley³⁸⁸)

Etiology and Pathogenesis Since inflammatory reactions in fibrous tissue are common to many "rheumatic" and other diseases, some writers do not without a pathologic basis, speak of fibrositis of rheumatic fever, of gonorrhea and so on (Telling⁵⁰²) Forms of fibrositis are undoubtedly a part of these diseases, but these are thought of as secondary fibrositis in association with a dominant, recognized clinical syndrome When writers speak of "fibrositis" they usually mean a primary form—disease of fibrous tissue independent of disease elsewhere Precipitating factors are given as influenza and respiratory infections, thermal and barometric changes, acute injury or chronic strain Actual causes are given as general or focal infections, "intestinal toxemia," "metabolic derangements," physical fatigue³³⁷ In many cases the cause is unknown Chilling and climatic change are regarded by some^{442, 502} as primary causes, but Buckley³⁸⁸ considers them only precipitants "Damp and cold will never cause more than passing stiffness in the absence of toxic substances, whether these are bacterial or metabolic in origin"

The pathogenesis of the disease involves an inflammatory exudate which may produce transient symptoms and then resolve If resolution does not occur, the exudate becomes organized and gives rise to nodules, cords or bands in muscles or large indurated areas with painful tender spots³³⁷

Symptoms The symptoms are pain, stiffness, soreness, tenderness of affected tissues, and sometimes spasm of related muscles Pain may be continuous or intermittent, sharp or dull Stiffness and pain are often worse on waking in the morning and after an hour or so of inactivity during the day, but lessen after moderate activity Such "jelling" is presumably due to the results of capillary congestion that accompanies inactivity and is relieved by some motion⁵⁰² Fibrositis may be diffuse, affecting various anatomic regions, but is usually localized Local varieties often have separate names as each has its special symptomatology, they are described by Alexander,³³⁷ Buckley,³⁸⁸ Telling,⁵⁰² and Willcox⁴⁴¹

Panniculitis may be widespread or localized to thighs or neck When the neck is affected aching pain occurs in the occipital region and extends over the vertex "fibrositic or indurative headaches" Telling considers them the commonest type of chronic or intermittent headache, "the four diagnostic features of which are persistency, thickening, nape-of-the-neck location, and tenderness" Pain is variably persistent and intense Many cases of pleurodynia, fibrositis of the chest, are diagnosed angina pectoris Certain vague abdominal pains are due to fibrositis of the rectus or other muscles In abdominal fibrositis pain and tenderness are elicited by "finger tip pressure" rather than by "flat-hand pressure", tender spots are more or less localized, but may be multiple and occupy positions not usually affected by visceral disease, muscle rigidity (usually present in the latter) is absent and pain may be intermittent and affected by weather

Perineural fibrositis generally affects brachial or sciatic nerves and is often called "neuritis," a misnomer unfortunately sanctioned by physicians. In "brachial perineuritis" there is tenderness over the brachial plexus above and below the clavicle and pain when the arm is abducted. Pain follows the distribution of nerves affected. "Brachialgia" may be associated with fibrositis of the subacromial bursa, deltoid muscle, or long head of the biceps. Many cases of sciatica are from perineural fibrositis, which may accompany lumbosacral and sacro-iliac disease and strain. Gluteal fibrositis may be present with or without sciatic fibrositis, as may lumbar fibrositis (lumbago) also. Telling believed there were more cases of fibrositic "trigeminal" neuralgia than of true trigeminal neuralgia.

The two commonest forms of fibrositis are the localized or diffuse intramuscular fibrositis ("myalgia," "neuromuscular pain," "muscular rheumatism"), and periarticular fibrositis ("arthralgia," "capsular rheumatism"). (Without further definition the term "arthralgia" has been used herein by several writers [Gray,²⁻¹ Monroe,^{-9c} Dreyer and Reed³³¹] who contrasted it with atrophic or hypertrophic arthritis. May one assume that periarticular fibrositis was present?—Ed.) Willcox⁴⁴¹ and Hench¹⁰⁶ emphasized the importance of differentiating the latter from "arthritis" which it is usually erroneously called. Symptoms of periarticular fibrositis are stiffness and soreness of joints, particularly after sleeping or resting, tenderness which is often evanescent, and pain often brought out only when the capsule is stretched. Symptoms are marked by variability and transiency but may be continuous. Differentiation from arthritis rests on persistency with which sedimentation rates, roentgenograms, blood counts, and weight curves are normal and on the general absence of muscle atrophy, deformity, and significant swelling. When "swelling" is present it is usually slight, localized and extra-articular, more of a "thickening" than actual swelling, and hydrops is absent (Hench¹⁰⁶).

Some writers make much of the nodules of fibrositis which to others seem "only accessible to the finger of faith." Because some consider it difficult to locate nodules or to demonstrate pathologic changes in tissues removed at biopsy, fibrositis has been defined as a "disease which physicians found but surgeons rarely find" (Telling⁵⁰²). Fibrositic indurations may be non-nodular (as strands, tracts, sheaths) or nodular. Of the latter there are presumably three kinds: large nodules (generally in fibrous aponeuroses), small nodules (generally in muscle bundles), and "myogeloses." The last are small sharply-localized areas of hardening in muscles, chiefly gluteal, which Lange (1931) and Nicola (1932) ascribed to local chemical disturbances, possibly local accumulations of lactic acid, and which are "negative" on biopsy. The nodular indurations consist presumably of inflammation of the perimysium and vary in size "from a pea to an almond" (Sutro⁵⁰³). Obvious visible nodules are the exception, not the rule as some have led themselves to expect⁵⁰². Cyriax⁵⁰⁴ believed that around most of the nodules are small localized muscular contractions, and that when

nodules rapidly "disappear" under various measures, it is the muscular contraction that disappears, leaving a residual nodule too small to palpate.

Pathologic Studies Such studies have concerned nodules more than other tissues. Nodules consist of "fibrous septa enclosing muscle fibers and bundles of characteristically vague and ill-defined outline," according to Telling⁵⁰² who stated that nodules of fibrositis are different in anatomy, pathology, and distribution from the nodular formations of rheumatic fever, which are "still further differentiated by being absolutely painless, even on palpation."

The small or fairly large subcutaneous nodules frequently found in sacro-iliac regions are regarded by many as evidence of fibrositis, active or old. They may be painless or painful depending on the stage of inflammation therein. Because they are often found in patients who give no history of fibrositis, some regard them as of no significance. Among 170 unselected hospital patients with various complaints Sutro⁵⁰³ found subcutaneous nodules, generally over sacro-iliac joints or near the tips of the lumbar spinous processes, in 94 cases (unilateral in 45, bilateral in 49). Thirty-three of the 170 patients had low backache, 10 had no nodules, and 16 had tender and seven non-tender nodules. Tender nodules were removed in four cases. One patient was a woman with low backache and sacro-iliac arthritis; she claimed complete relief after nodules were removed. One was a patient with subastragalar tuberculosis and no backache. One patient had a low backache and sacro-iliac arthritis, the backache persisted after operation but local tenderness disappeared. One patient had a low backache, sacro-iliac arthritis and no postoperative relief. Examination of the nodules in these four cases showed them to consist of lobules of adult fat of normal appearance without signs of recent or old inflammation or other evidence of metabolic or toxic disturbance. Sutro concluded that they were "protective buffer-pads over poorly muscle-covered areas of sacrum and ilium," that they were not part of any recognized disease and may be found in apparently normal persons, and that they were wholly different from those of rheumatic fever, atrophic arthritis, and syphilis.

(This study represents a laudable beginning but does not settle the issue. The relief which two of the four patients obtained by removal of nodules is not explained nor is the tenderness of the nodules. Many more nodules in various stages of tenderness and formation should be examined, as well as sections of adjacent fibrous tissue. It is difficult to believe that such nodules are "normal" even if they are often symptomless and in patients who give no history of fibrositis—Ed.)

Laboratory Data Of 68 patients, 36 per cent had an abnormal levulose tolerance test²⁹¹. In five cases the average values for albumin, globulin and total protein of blood were a little below normal²⁵⁷. Blood groups were normally distributed²⁶⁰.

Treatment This follows the same general principles as in atrophic arthritis. Removal of foci is advised^{388 502}. Vaccines seemed valueless to some,³⁸⁸ helpful to others¹⁰⁶. Buckley³⁸⁸ considered protein therapy useful,

and for empiric reasons advised the use of onions and garlic in diet. In some cases the affected part must be rested with slings and strapping, but rest is not indicated for fibrositis of neck and chest, according to Telling.⁵⁰² Various forms of physical therapy were employed³³⁷ short wave diathermy,^{17, 18, 356, 505} Fango,³⁵² histamine ionization,^{17, 320, 388} paraffin baths, pelvic diathermy⁵⁰⁸ and fever therapy^{48, 74}. "The only curative therapy" is massage, according to many^{254, 502}. Massage should be light over affected tissues, except nodules "which can be rubbed away"³⁸⁸. Tender nodules were surgically removed by Stockman⁵⁰⁷. For associated fatigue, glycine (amino acetic acid) has been tried with variable results.⁵⁰⁸

Epidemic Myalgia Carney⁵⁰⁹ saw 87 cases of epidemic pleurodynia in one month in West Virginia. Typical symptoms were fever, rapid pulse and respiration, pain at the attachment of the diaphragm to the anterior abdominal wall, or at times in the epigastrium. Pain was greatly aggravated by respiration. The disease usually ended in about 24 hours. A plasmodium was suspected.

Noting the frequency with which persons suddenly developed one-sided "stiff neck," Massell and Solomon⁵¹⁰ questioned 61 patients and 52 hospital colleagues who had recently suffered therewith. Symptoms were usually noted on waking, were occasionally gone by noon, generally lasted one to two days subacutely, and in some cases hung on mildly for several days or weeks. Sites of maximal pain in order of frequency were the origin of the trapezius muscle at the superior nuchal line, half way down the neck along the border of the trapezius, at the insertion of the sternocleidomastoid muscle, and at the lower border of the trapezius at the shoulder. No nodules were felt. Heat gave relief, massage was painful but gave more relief. Treated patients had the condition as long as the others, however. A hypothetical "twist of the neck while asleep" or "exposure to draft" did not seem as likely a cause as an epidemic infection, suspected but not investigated. The attitude of physicians to "epidemic benign myalgia" should not be the same as that of patients—one of annoyed tolerance and resignation.

(The inquiry, being mostly of the questionnaire type, did not escape the inadequacies inherent therein—Ed.)

Myositis Ossificans Three types were mentioned (1) progressive, (2) circumscripta, (3) post-traumatic. Studies on a patient with the progressive type convinced Wilkins and his colleagues⁵¹¹ that phosphatase is intimately associated with the ossification. At various stages of the disease biopsies were made on normal and affected tissues. Serum calcium, plasma phosphatase, and inorganic phosphorus were normal. Total and inorganic phosphorus of diseased muscle was much lower than in normal muscle. The phosphatase activity of affected muscle in the pre-ossification stage was 800 to 1,600 times that of normal muscle, and several times that of normal bone, that of heterotopic bone was much higher than that of normal bone.

Features of a case of traumatic myositis ossificans, reported by Taylor, Shea and Argyr⁵¹² included contusion, swelling, induration, limitation, tenderness and palpation of a hard mass which could be rotated around the bone shaft. Serial roentgenograms reveal a mass of increasing density separated from the bone shaft. As density increased the mass showed lamellae corresponding to ossification of muscle bundles or fascial layers. Osteogenic sarcoma is differentiated from myositis ossificans in that the former progresses instead of regressing after four to six weeks, is usually near the epiphysis, and becomes connected with the bone. Treatment of traumatic myositis ossificans includes rest, heat to promote absorption of the hematoma, and excision if function is disturbed.

Chronic Generalized Fibromyositis (Progressive Myositis Fibrosa) Few cases have been reported. In one case recorded by Ornstein⁵⁰¹ hardness and stiffness of muscles of limbs, back and abdomen, severe muscle spasms, myotonia, sweats, rapid respiration and pulse, and loss of weight of one year's duration were present. Creatinuria was absent. Biopsy of muscle showed a marked increase in subcutaneous fibrous tissue and severe scattered degenerative changes in many muscle cells. "Absence of skin lesions differentiated it from dermatomyositis." The differential diagnosis and a review of reported cases were discussed.

Dermatomyositis This was the suggested diagnosis in a case seen by McAlpine⁵¹³. Pain behind the knees, and later diffuse swelling of legs, hands and forearms were present. These subsided and progressive stiffness and weakness of the hands ensued. Muscles of the hands, forearms, and legs and the rectus muscle were hard. Leukocytes numbered 14,500 to 18,000 per cu mm blood, eosinophiles comprising 33 to 37 per cent. Biopsy revealed increases in sheath nuclei but no giant nuclei, Trichinella or marked inflammatory infiltration.

Miscellaneous Myopathies Features of myasthenia gravis and various muscular atrophies were reviewed by Ains and Cobb⁵¹⁴. Myopathies can be separated into two groups, according to Milhorat and Wolff⁵¹⁵ (1) those in which creatinuria is marked and creatine tolerance grossly deficient, a deficiency exaggerated by the administration of glycocoll, and (2) those in which creatinuria is slight and the creatine tolerance is slightly deficient and not exaggerated with glycocoll.

Traumatic Injuries to Muscles and Tendons Clinical features and differentiation of various traumatic lesions were described by Haldeman and Soto-Hall⁵¹⁶. Symptoms common to most ruptures were sudden sharp pain or "snap" during violent effort, inability thereafter to perform certain motions, and the appearance of ecchymoses and a defect in muscle or tendon. A lightly-exposed roentgenogram may show a defect in muscle shadow or a chip of bone torn from a tendon insertion. Application of faradic currents to a ruptured muscle causes it to contract with pain at the site of tear. Injections of procaine hydrochloride into the subdeltoid bursa helped to dif-

ferentiate between bursitis with reflex spasm of the supraspinatus muscle, and tears of the supraspinatus tendon. If the former is present the arm can be abducted actively and painlessly a few minutes after injection, if the latter is present active abduction is not improved. In the lower extremity the quadriceps, and in the upper the supraspinatus, muscle or tendon is most likely to be torn, especially in the supraspinatus muscle, degenerative changes of advancing age (fibrillation or fraying, even perforation of the supraspinatus tendon into the joint) play a predisposing rôle.

Subdeltoid Bursitis This results from trauma more often than from allergic, toxic or infectious agents, in Palmer's ⁵¹⁷ experience. Diathermy was most helpful if small rounded electrodes were used and properly placed. Rest and ultraviolet irradiation were also used. Of 65 patients, 32 were men, 33 women, the age incidence was 25 to 71 years. Forty-seven patients who were relieved received an average of 16 treatments. Patients with calcified subdeltoid bursitis (post-traumatic?) were frequently notably relieved when Haldeman and Soto-Hall ⁵¹⁶ injected 10 to 15 c.c. of 1 per cent procaine hydrochloride into the bursa. Calcium deposits sometimes disappeared within a few days. Often no other treatment was necessary. Injections were sometimes repeated. (Such calcium deposits sometimes rapidly disappear spontaneously—Ed.) Others advocated short wave therapy, ^{518, 519, 520} histamine iontophoresis, ^{517, 520} massage and manipulation ⁵¹⁰

MISCELLANEOUS CONDITIONS

Bunions Bunions may seem of minor importance, but they are painful, crippling, deforming and unsightly. Stanley and Breck ⁵¹⁸ operated on 211 bunions (129 patients) by the Petersen-Fowler-Singley procedure—a web-incision between the great and second toes. After backward and mesial disarticulation of the great toe the exostosis was removed with "uniformly good results." In 20 years' experience no patient needed a second operation or complained of a poor result. (They were California State prisoners—Ed.) The operation had these advantages: the technic is simple and trauma slight, the scar is not exposed to subsequent trauma from shoes, the weight-bearing buttress of the joint is undisturbed, the period of disability is minimized and danger of ankylosis is negligible.

Osteopoikilosis (Bone Speckles) This represents an asymptomatic familial anomaly of bone discovered accidentally in roentgenograms. Small circumscribed areas of increased density (2 to 5 cm. in length) may appear almost anywhere in the skeleton. In some cases dark vertical striations giving shadows much denser (less opaque) than normal bone are seen. Sutherland ⁵¹⁹ reviewed the 32 reported cases and discussed the relation of osteopoikilosis to melorheostosis and chondiodysplasia. (An additional case was presented, that of a young man with multiple areas of circumscribed mottling in many bones. Linear striations [10 mm. long, 5 mm. wide] were also seen in diaphyses of tibia and fibula. Blood calcium, phosphorus and phosphatase were normal. His mother and a brother were similarly affected—Ed.)

Multiple Myeloma Cases of myelomatosis may present features resembling hyperparathyroidism. Such a case was seen by Enzel and Lieberman.²⁰ An elderly man developed low backache and lost 30 pounds (13.6 kg). Marked emaciation, a tender lumbar spine and sacro-iliac joints, and Heberden's nodes were noted. Roentgenograms revealed multiple areas of bone destruction in spine, pelvis and femurs, and (unrelated) hypertrophic arthritis. Bence-Jones albumose was not found (one test). Blood calcium was 11.8 to 13.7 mg and phosphorus 3.2 mg per 100 c.c. A negative calcium balance was present (in the diet 200 mg, in urine 530 mg). Hyperparathyroidism was suspected, but at operation no tumor was found. Postoperative pneumonia was fatal. Necropsy revealed myelomatosis and marked parathyroid atrophy (presumably from functional hyperparathyroidism).

Differentiation Cases of hyperparathyroidism generally have an elevated serum and urinary calcium, a normal or low serum phosphorus. Sometimes serum calcium is normal. In myelomatosis hypercalcemia may also appear, but serum phosphorus is generally normal or high. Serum phosphatase is generally high in hyperparathyroidism, normal with myeloma. Bence-Jones albumose is not always present in myelomatosis and may be present in other diseases (including hyperparathyroidism^{47,48}). A negative calcium balance may be present in both. Differentiation, therefore, may be difficult and should be made only after comprehensive, and not superficial, clinical, chemical, radiologic and metabolic studies, with biopsy if necessary.

PHYSIOLOGY OF ARTICULAR TISSUES

Collins²¹³ found that, in general, the chemistry of synovial fluid is the same as that of the patient's blood. Differences in sugar and protein concentrations may be found. Synovial fluid sugar is apt to be much lower than blood sugar in cases with infected synovial fluid but not in those in which fluid is sterile even though it has a high cell count. Thus a synovial sugar of 50 mg or more below the blood sugar level is strong evidence of bacterial invasion of the fluid. Total proteins are increased in most effusions, especially with many cells. Consistent increases in protein and cell count in fluid in atrophic arthritis indicate an exudate, not a transudate, is present. Studies on synovial cytology were more helpful than those of synovial chemistry. Six types of cells are commonly found: polymorphonuclears, eosinophiles, lymphocytes, monocytes, macrocytes (large phagocytic cells) and synovial lining cells. The total cell count and percentage of polymorphonuclear cells vary in different diseases (table 2). Whereas the normal synovial fluid contains "about 200 cells" per cu. mm. of which less than 10 per cent are polymorphonuclears, joint fluid in atrophic arthritis contains 5,000 to 60,000 nucleated cells, of which generally 70 to 90 per cent are polymorphonuclears. Total and differential counts were much lower in hypertrophic than in atrophic arthritis, and only slightly altered in intermittent hydrops and in "sympathetic joint effusions"—with inflammatory lesions near but not in joints. (Collins' more extensive data have since appeared.⁵²¹—Ed.)

TABLE II
Studies on Synovial Cytology (Collins²⁷³)

Condition	Cases studied	Total nucleated cells, per cu mm synovial fluid		Polymorphonuclear leukocytes, per cent	
		Usually	Range	Usually	Range
Normal		"About 200"		Below 10	
Atrophic arthritis	35	10,000-20,000	5,000-60,000	70-90	40-100
Hypertrophic arthritis	4	Below 1,000	Below 1,000-10,000	Below 10	0-20
Gonorrheal arthritis (sterile fluids)	4		5,000-30,000		30-80
Intermittent hydrops	1 (two samples)		1,600, 2,500		58, 78
"Sympathetic joint effusion"	2		Below 1,000		0-20

Warren, Bennett and Bauer⁵²² studied the synovial fluid at necropsy of 150 persons who had died of miscellaneous conditions and had had no joint symptoms. Synovial cytology may be unaltered, though the patient has a marked leukocytosis. Cartilage defects and débris may increase the nucleated cells and percentage of phagocytes. The total nucleated cell count per cu mm is reduced in synovial effusions in edematous patients. Patients dying with any severe infection (without joint symptoms) sometimes have a high, synovial total cell count and polymorphonuclear leukocytosis.

Leukocytes contain proteolytic (tryptic) ferments which, in sufficient amounts, can destroy articular cartilage. To prevent leukocytes in synovial fluid from doing this, synovial fluid contains antitryptic substances which inhibit tryptic digestion (Holmes, Keefer, Myers^{523, 524}). These antitryptic substances (which can be removed from synovial fluid by extraction with chloroform) probably come from blood plasma, as their concentrations in fluid and plasma are similar. Synovia cannot protect cartilage adequately when its antitryptic powers are reduced in the presence of effusions containing large numbers of cells, especially polymorphonuclears, for from such effusions, particularly purulent exudates, proteolytic enzymes are liberated in great amounts. (Hence the necessity of draining purulent or suspected purulent effusions promptly to prevent or minimize cartilage destruction—Ed.) Nevertheless, synovial fluid is apparently able to prevent or inhibit cartilage destruction even when the synovial fluid contains as many as 20,000 leukocytes per cu mm, for it was found that although cartilage destruction occurred *in vitro* in the presence of synovial fluid in two cases of staphylococcic arthritis in which synovial fluid cells numbered 110,000 to 240,000 per cu mm, car-

tilage destruction did not occur in the presence of synovia in seven cases of gonorrheal arthritis with 7,850 to 21,000 cells per cu mm of synovia, or in three cases of tuberculous arthritis with synovial counts of from 6,500 to 11,600 cells

To study healing processes in joints, Bennett and Bauer⁵⁻⁵ compared the processes of cartilage repair in adult dogs to those in young dogs in which epiphyseal union had not yet occurred. Defects of central, non-weight bearing articular cartilage were produced surgically. Repair of these defects was no more rapid or complete in young dogs than in adult dogs. In both, healing was slow: none was noted after four to 12 weeks, it was notably present but incomplete after 20 to 28 weeks. Repair occurred in three ways: (1) an independent proliferation of original cartilage cells, this was greater in the deeper zones of articular cartilage than in the more superficial zones, (2) proliferation of vascular tissue from perichondral margins, (3) when subchondral marrow spaces were involved in the surgical defect there was also an ingrowth of vascular connective tissue therefrom. Repair (active proliferation of cartilage cells) occurred most satisfactorily when the defect extended into subchondral bone (in which case granulation tissue from marrow spaces gradually filled the defect), or in crevices where cartilage was protected from friction. The latter would indicate that function may inhibit repair. Bennett and Bauer were unable to corroborate the opinion of Key (1931) that such defects in articular cartilage may be an important cause of intra-articular disease. Associated intra-articular disease was found only in joints where patellae became displaced.

Studies on the comparative value of four dyes used for the arthrographic diagnosis of joint mice, cysts, semilunar injury and so forth, were made by Keller^{62a}. For diagnostic purposes the ideal dye should produce sufficient opacity for roentgenographic detail, a minimum of discomfort and reaction after injection, and be eliminated rapidly enough to avoid irritation as a foreign substance but not too rapidly to prevent painstaking radiologic studies. All four dyes used produced satisfactory opacity, but hippuran gave the mildest post-injection reaction, a sense of fullness without pain, and it was therefore preferred. It disappeared from joints in three to four hours. After administration of arthrospin articular pain lasted a few hours (time unstated), after neoipax three to 10 days, after skiodan it was severe and lasted over two weeks. Some patients with "chronic arthritis" noted improvement in the injected joint after the post-injection reactions. Therefore if one wishes to attempt a therapeutic as well as diagnostic procedure, arthrospin was recommended. It disappears from normal joints in 17 to 24 hours, sooner from joints subacutely inflamed, much slower from joints with thickened capsules. Use of these dyes is presumably contraindicated for patients with liver or kidney disease or hyperthyroidism. Arthrospin contains 68 per cent iodine, and is a 10 per cent solution of the disodium salt of tetraiodo-ortho-sulpho-benzoate.

The Golgi apparatus appears as reticular material in almost every cell of all animals. Its nature is uncertain. Some consider it an artefact, but it has been observed in living cells. Others regard it as indicating an area of protoplasm which is the site of special activities. Whatever it is, this "apparatus" is a morphologic component of cells demonstrable in certain circumstances and altered by environmental changes that affect other parts of the cell only slightly or slowly. Thus when tissues are removed from the body the Golgi material disappears before there are any (other) visible autolytic changes. In mild degenerative conditions in which the blood supply is impaired or disintegrative changes are present in cells the Golgi apparatus is grossly altered or absent. Never noted previously, a well-developed Golgi apparatus comparable with that of other connective tissue cells was demonstrated by King⁵²⁷ in synovial tissues of humans, horses and dogs. The apparatus becomes enlarged in conditions with increased synovial fluid. Cells, including synovial cells, free in synovial fluid also show the apparatus. Since it is not demonstrable in degenerative states, its well-developed character in synovial cells indicated to King that synovia is not a product of degeneration as some contend. Since the Golgi bodies of synovial cells are enlarged in inflammatory conditions he suggested that the enlarged apparatuses indicate secretory activity of synovial cells. (A good review of synovial histology was given—Ed.)

Allen⁵²⁸ noted that non-particulate solutions (methylene blue and trypan blue) escaped from knee joints of live cats and appeared in iliac lymph nodes in one to four minutes, but that particulate matter (India ink, erythrocytes) did not appear in nodes for three to five hours. Experiments were then done on perfused kittens just after death. Muscular contraction, joint involvement and increased joint tension caused more rapid passage of fluid and particulate matter from joints to lymphatics. Certain bacteria were injected directly into joints and subsequent cultures of blood and lymph nodes were taken. Animals allowed to move around had a tendency to show more positive blood cultures than those whose joints were fixed in plaster. Allen interpreted these results as evidence that immobilization of infected joints is desirable to prevent spread of infection.

A method for measuring and recording joint function was reported by Cave and Roberts,⁵²⁹ and Moore⁵³⁰ described an apparatus for articulometry of feet.

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The chairman of the editorial committee for this review will welcome the receipt of reprints from authors of current (1936-1937) articles which will greatly facilitate the preparation of subsequent reviews

CASE REPORTS

EXTRAPYRAMIDAL SYNDROME AND ENCEPHALOGRAPHIC PICTURE OF PROGRESSIVE INTERNAL HYDROCEPHALUS IN CHRONIC HYPOLYCEMIA

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IN the past decade since the description of the syndrome of spontaneous hypoglycemia or hyperinsulinism, numerous cases have been recognized and reported. The variegated symptom-complex has become more definitely delineated and a number of comprehensive reviews of the subject have appeared¹. The neuropsychiatric symptoms of hypoglycemia are among the most interesting, and have received special attention by Stone² and others.

The purpose of this communication is to record a case of chronic spontaneous hypoglycemia which has been studied over a period of 16 months of hospitalization. The outstanding features included convulsive seizures, hypoglycemia, and a persistent extrapyramidal syndrome with encephalographic evidence of progressive internal hydrocephalus.

CASE REPORT

History H L , a white male, aged 49 years, was admitted in a comatose condition to the Neurological Service of the Mount Sinai Hospital on February 16, 1934.

The familial and past history were essentially negative. He had followed various forms of employment, including that of a painter for a short period, until June 1933 when he began to suffer from weakness, tiredness, mental depression, and attacks of dizziness. One month later, he began to have periods of unconsciousness accompanied by abnormal movements and rigidities in the extremities. During these episodes his breathing became noisy and saliva drooled from his mouth. The entire attack lasted from one to three hours, recovery was spontaneous. On regaining consciousness he complained of headache and was unable to recall any of the preceding events. There was no aura, he did not cry out at any time, did not bite his tongue, nor was there incontinence. These episodes recurred at intervals of about a month, and were not noted to occur at any particular time of the day. During the eight months preceding his present admission his speech became slower and thicker, he seemed to have difficulties in articulation, his vision and hearing became impaired, and micturition became more frequent, without polydipsia. A change in his personality was noted by his friends and relatives, he became morose, depressed, asocial, preoccupied, disinterested in his surroundings and definitely detached from his former activities.

On two occasions he was admitted to the neurologic service of another institution (October 22 to November 14, 1933, and from January 12 to February 13, 1934), where a cerebral neoplasm was suspected, but no definite diagnosis could be made. An encephalogram on each admission showed mild cerebral atrophy but failed to show deformity or displacement of the ventricular system. Two blood sugar esti-

* Received for publication April 16, 1936.

From the Neurological Service of Dr Israel Strauss, Mount Sinai Hospital, New York, New York.

mations were reported as 189 mg per cent and 42 mg per cent respectively. Other clinical and laboratory studies were essentially normal.

Examination showed a well developed and well nourished adult white male in a semi-stuporous condition. The systemic examination was essentially negative. The blood pressure was 140 systolic and 90 diastolic. The positive neurologic signs included hyperactive deep tendon reflexes which were more marked on the left, absent superficial reflexes, Hoffman reflex positive on the left and inconstant on the right, Babinski sign positive on the right and equivocal on the left, and a slight weakness of the left lower facial musculature. The pupils were equal and reacted promptly to light. The fundi oculi were normal. A lumbar puncture revealed clear fluid under a pressure of 120 mm of water. The Queckenstedt test was negative. After the removal of 10 cc of fluid the pressure dropped to 40 mm. The stupor persisted and irregular convulsive movements appeared. Fifty cc of 50 per cent dextrose were then administered intravenously, without effect. The convulsive movements and stupor continued for another three hours, when he gradually began to respond. The following morning (12 hours later) he was mentally clear.

The diagnoses considered on admission were brain tumor, presenile dementia (Alzheimer's disease), or subacute encephalitis. On April 2, 1934, to rule out a brain tumor, an encephalogram was performed, following which he became stuporous and showed a recurrence of the convulsive semi-purposeful movements. A blood sugar estimation at this time was 45 mg per cent. Following the intravenous administration of 70 cc of 50 per cent glucose, he regained consciousness, responded to questions and began to complain of headache. The diagnosis of hypoglycemia became probable and was confirmed by the subsequent course.

The course and data are best presented under separate headings.

(a) *Hypoglycemic Seizures*. The hypoglycemic seizures were the outstanding manifestations of the illness. During a period of 14 months, 130 seizures were observed (table 1). The seizures occurred at all times of the day, but a majority were in the afternoon.

TABLE I

The distribution and frequency of the attacks are tabulated. During July, the patient was receiving foreign protein fever therapy. The lower part of the table shows the greater frequency of the attacks during the afternoon.

<i>Month</i>	<i>Number of Attacks</i>
April 1934	7
May	19
June	26
July	0
August	6
September	8
October	16
November	4
December	10
January 1935	8
February	8
March	8
April	6
May	1
Total number of attacks	130

<i>Period of Day</i>	<i>Number of Attacks</i>
12 m to 6 a m	10
6 a m to 12 Noon	18
Noon to 6 p m	77
6 p m to 12 Noon	25

A seizure was preceded by apprehensiveness and irritability, the patient expressed ideas of hopelessness, said that he was going to die and became very uncooperative. He then became drowsy and stupor gradually supervened. The breathing became stertorous and noisy and bizarre convulsive movements set in. The movements were clonic and had a semi-purposeful character: these were groping of the hands, thrashing of the arms, treading motions of the legs, and turning movements of the body. The movements were irregular, involving either the whole body, one side, or even single limbs, but at no time was there a cortical spread of the seizure. The eyes were closed and the mouth drooped, and sometimes the head would roll from side to side. There were no clonic movements of the jaw, or biting of the tongue or lips. There was a marked increase of salivation but as a rule no frothing at the mouth. As the attack continued considerable amounts of saliva would drool from the mouth, and on one occasion 250 c.c. of saliva were collected within a period of one and one-half hours. Unconsciousness was complete, but the pupils continued to react to light. The tendon reflexes were usually hyperactive and occasionally showed some inequality. A Babinski sign was frequently elicited, but this was inconstant and varied from side to side.

At times, particularly in the later period of observation, "minor" attacks without convulsive movements would occur. These were characterized by lapses in which he would become drowsy, restless, and would assume a vacant expression and blink his eyelids. His responses were automatic, and no mental contact could be made. These attacks would last from a few minutes to one-half hour.

If not ended by an intravenous injection of glucose, the "major" attacks continued for two to three hours. He would then recover spontaneously without the ingestion or injection of any nutriment. Following these spells he was completely amnesic for the events occurring during or immediately preceding the seizure. The attack could always be aborted immediately by the intravenous injection of dextrose. He was usually given 50 c.c. of 50 per cent dextrose intravenously, but relief could be obtained with as little as 5 c.c. of 50 per cent dextrose. Figure 1 C shows the effect on the blood sugar of intravenous glucose administered to relieve two hypoglycemic seizures. Normal saline intravenously in similar amounts had no effect. Sweetened orange juice by mouth usually prevented an attack when given at the time when restlessness appeared, but administered through a stomach tube when the patient was unconscious, caused but little response. Hypodermoclysis or proctoclysis of 5 per cent glucose was no more effective than glucose by mouth. Epinephrine (1 c.c.), pituitrin (1 c.c.), and Collip's diabetogenic pituitary extract,*³ as well as many other glandular preparations were ineffective in relieving an attack.

Blood sugar estimations (total reducing substance) during seizures were as low as 30 mg. per cent. However, a low blood sugar was not invariably associated with a hypoglycemic attack. The correlation between the blood sugar and the condition of the patient is shown by figures 1 A, B and C.

During the hypoglycemic seizure the blood pressure usually increased slightly but at times decreased, the secretion of saliva increased, the ocular tension (by quantitative measure) decreased, and the blood cholesterol was decreased. The electrocardiogram showed minor changes as inversion of the T_1 and T_2 waves, and sinus tachycardia.

An attack could not be precipitated by 10 units of insulin administered subcutaneously about one hour after recovery from a seizure. Induced alkalosis by hyperpnea for three minutes was followed by a long period of apnea but no other changes. An attack was invariably induced by starving, particularly by eliminating

* This extract, which will raise the blood sugar in a Houssay dog, was kindly furnished expressly for clinical trial on this patient by Dr J. B. Collip of McGill University, Montreal, Canada.

breakfast, and often by the omission of the sweetened orange juice which he was taking every two hours

(b) *Neuropsychiatric Symptomatology* The course was marked by the progressive and permanent establishment of extrapyramidal and cortical signs. His stance became stooped slouching, and more and more like that of a Parkinsonian. The gait was slow and stiff with a gradual diminution and finally a complete loss of associative movements of the arms. He later showed repulsive tendencies. His hands became tremulous and a perioral tremor developed. The tremor of the fingers

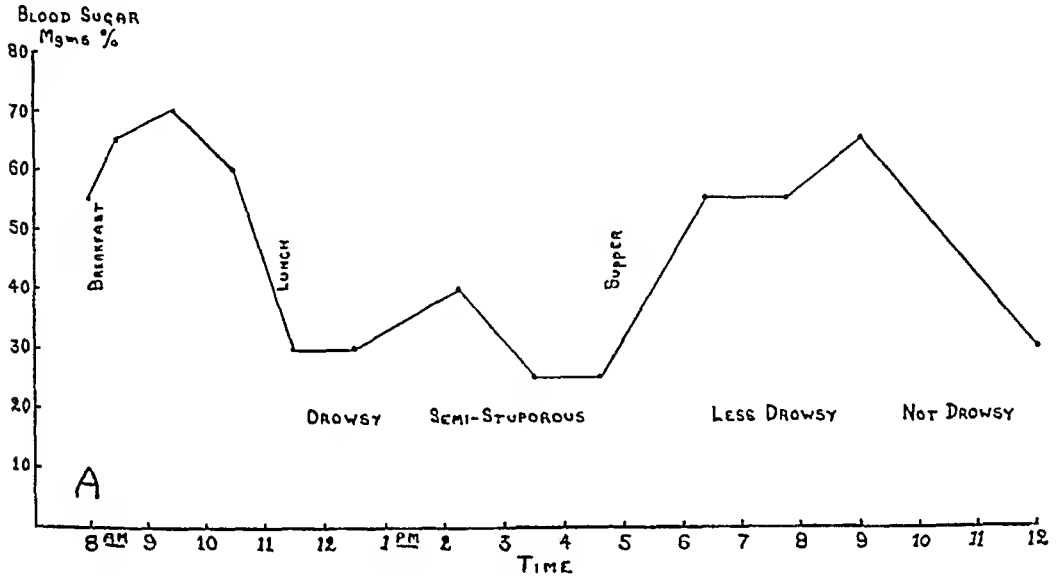


Fig 1 A

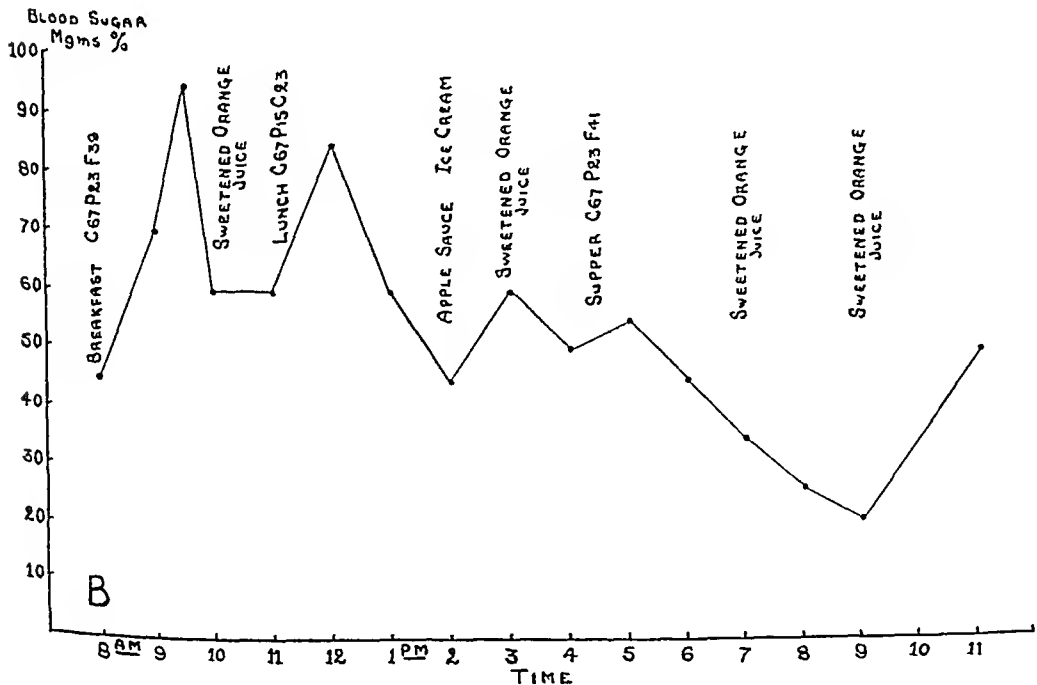


Fig 1 B

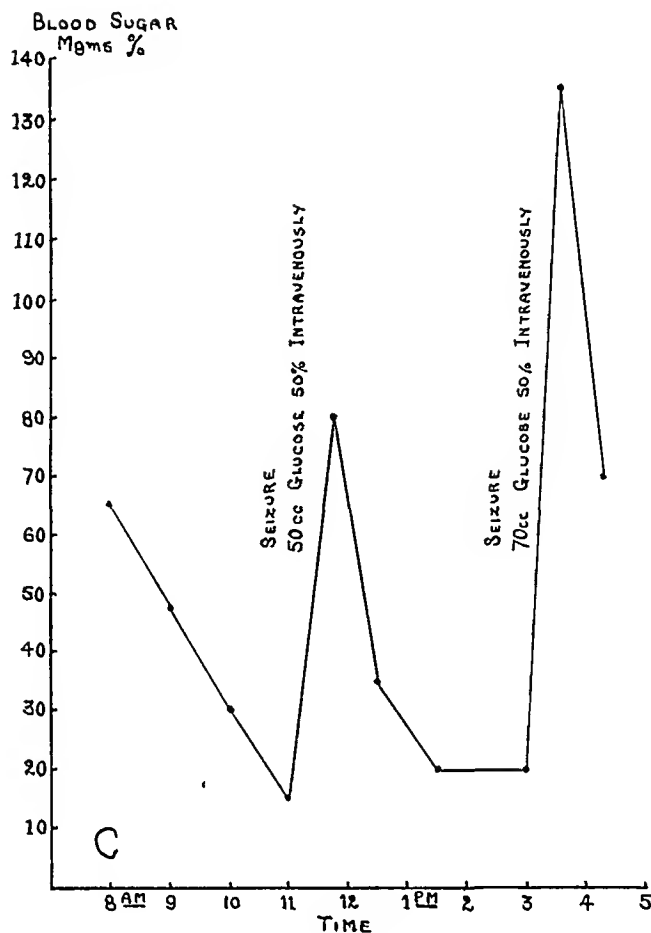


Fig 1 C

FIG 1 A, B AND C Graphs of blood sugar values estimated at frequent intervals throughout the day. There was no strict parallelism between the blood sugar values and the symptoms of hypoglycemia. Intravenous glucose was followed by a sharp rise and fall of the blood sugar.

was coarse and arrhythmic. On the finger to nose test he showed a slight intention tremor. Bilateral adiadochokinesis was noted early in his course. From day to day the speech became more and more dysarthric, thick, slow, syllabic, whining and, especially preceding an attack, was unintelligible.

The cranial nerves, except for hearing, were not involved. The fundi showed no changes, and repeated visual field examinations were normal. Visual acuity was O D 20/30, O S 20/70. The pupils were equal, regular and reacted well to light and accommodation. No weakness of the external ocular muscles was noted. Two months after admission, the patient complained of impaired hearing in the right ear, and this progressed to involve both sides. The hearing defect was found to be of the nerve type. The levels of both the upper and lower tones were markedly diminished, the upper tones being more involved. The deafness was more marked in the right ear. Immediately preceding discharge from the hospital he could not hear the tick of a watch placed 1 cm from the ear, when it was heard by the examiner at two feet, when placed against the ear, it was audible. Vestibular function as tested by the response to caloric (cold) stimulation, was normal.

The motor power became progressively weaker. The muscles showed increased myotatic irritability. During several hypoglycemic attacks coarse fibrillations were noted in the right forearm. The tendon reflexes were generally hyperactive, and showed inconsistent variations from day to day. Definite pathological reflexes, as the Babinski sign and other confirmatories were noted from time to time varying from side to side, but these were not persistent.

Sensation was not affected except for a short period four months after admission. At that time he began to complain of paresthesias in his hands and feet, and these gradually involved the forearms and legs. On examination he showed sensory diminution of all modalities in typical glove and stocking distribution. Within three months these signs and symptoms disappeared spontaneously. Apparently there was a transient attack of symmetrical peripheral neuritis.

The *mental condition* was one of progressive intellectual and emotional deterioration. He was completely amnesic regarding the seizures and on recovery from each often showed a short period of confusion. For two weeks in the early period of his observation he showed delusions of persecution and ideas of reference. He thought that the nurse wanted to poison him, that people were taking pictures of him, and he openly accused a number of other patients on the ward. He did not elaborate on these ideas and was irritable and belligerent. He later regained partial insight and reluctantly admitted that it was a product of his imagination.

His interests were minimal and gradually became fewer. He was content to sit by himself, and made few contacts with the other patients. He soon became incapable of coherent speech and his verbal productions were limited to a few requests regarding his immediate needs. When conversation was attempted he used few words and was often simply monosyllabic. When clear he was cognizant of his illness. He knew that he had low blood sugar and frequently reminded the nurses that his orange juice was due. He realized that he was permanently handicapped and that he would be unable to earn a living so that his general attitude was pessimistic, although he frequently appeared euphoric. At times he was facetious in a simple way and smiled even in irrelevant situations. At other times he became depressed emotionally unstable, and expressed fears that he would never be healthy. As previously stated an hypoglycemic attack was preceded by anxiety, apprehensiveness and irritability. His intellectual capacities showed progressive diminution. His memory became impaired both for recent and remote events. As a rule he had good insight into his somatic condition but not regarding his mental defects. His judgment was impaired.

(c) *Systemic and Laboratory* The systemic examination showed no unusual changes except for an increase in weight. On admission he weighed 152 pounds and a year later he had gained 21 pounds. The blood pressure varied from 130 mm of Hg systolic and 90 diastolic to 160 systolic and 100 diastolic. The numerous laboratory investigations showed very little of significance except those referable to sugar metabolism. The urine was normal and never showed any sugar. Special tests for lead in the urine were negative. The hematologic examination was normal. The cerebrospinal fluid sugar was 15 mg per cent. The blood cholesterol during an attack was decreased to 105 mg per cent. The Rehfuess gastric analysis showed a good acid curve with levels of total acid of 58 and of free HCl of 42, no blood or other abnormalities were noted. The stools were normal. The galactose tolerance test for liver function was normal and no sugar was excreted in the urine. Glycogen storage was deficient as there was no notable increase in blood sugar to epinephrine. The basal metabolic rate was plus 6 per cent. An electrocardiogram showed regular sinus rhythm, left ventricular predominance, and an inverted T_2 wave. During an attack the electrocardiogram showed sinus tachycardia and inverted T_1 and T_2 waves. The roentgen-ray of the skull, and a gastrointestinal series were negative.

(d) *Blood Sugar* The Folin-Wu method modified for the estimation of low values was used for the venous blood sugar determinations. The fasting blood sugar

varied from 30 to 45 mg per cent. On two occasions, when allowance was made for the non-glucose reducing substances in the blood (estimation following yeast fermentation of glucose as compared to a non-fermented specimen), the fasting sugar values were 5 and 7 mg per cent respectively. These low sugar values as previously stated were not invariably associated with hypoglycemic seizures.

The Janney sugar tolerance test was performed 10 times during the period of observation (figure 2). As shown in the graph, the blood sugar level continued to rise for the first hour, rested at this level for about one hour, and then dropped to a point lower than the original fasting level. During the plateau-like period of high blood sugar value, a trace to 14 per cent sugar was noted in the urine on several occasions. Figure 1 *A* and *B* illustrate the diurnal course of the blood sugar while on a regular diet with additional glucose in the form of orange juice. Note that the values of blood sugar decrease in spite of the ingestion of food. Epinephrine and

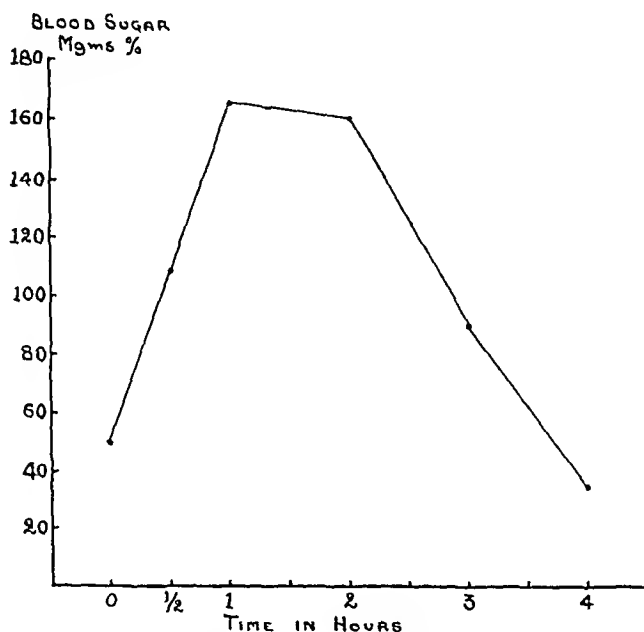


FIG 2 Blood sugar tolerance curve (from average values of ten tests)

antuitrin tolerance tests demonstrated no significant alteration of the fasting blood sugar curves.

(c) *Encephalogram* Several encephalographic studies were carried out and these showed progressive cerebral pathology. The first encephalogram (figure 3) on April 2, 1934 was reported as "Both lateral ventricles symmetrical, moderately dilated and in the midline. In the posterior horn there is a shadow which protrudes into the ventricular region which I believe is not pathological. The third ventricle is dilated and in the midline. The iter and fourth ventricle are also slightly dilated. The basilar cisternae are somewhat enlarged, and on some of the films there is evidence of air in the subtentorial region. Subarachnoid markings are not evident." This encephalogram was essentially similar to two others obtained previously one and four months respectively at the other institution. The encephalogram was repeated on March 29, 1935, and the principal change was an increase in the size of the ventricles (figure 4) indicating *progressive internal hydrocephalus*.

(f) *Treatment* Both as a diagnostic and therapeutic measure, an exploratory laparotomy was performed on May 12, 1934, by Dr A. A. Berg. The pancreas,

adrenals and liver were examined and were found to be normal. Biopsy specimens were removed from the liver and pancreas, and histological examination showed no unusual features.

A great variety of other therapeutic measures was investigated. Since none of these seemed to have any appreciable effect on his condition, they are only mentioned.



Fig 3 A

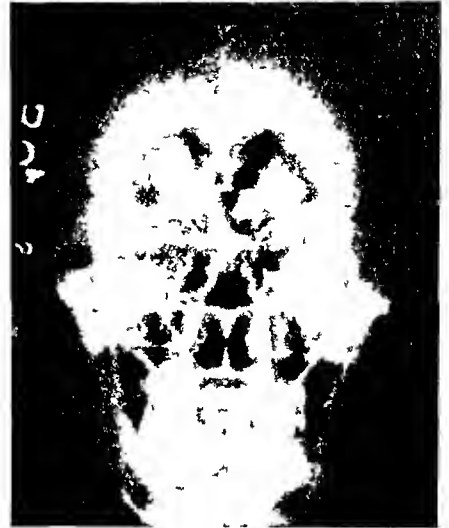


Fig 3 B

FIG 3 A AND B Encephalogram on April 2, 1934, showing internal hydrocephalus



Fig 4 A



Fig 4 B

FIG 4 A AND B Encephalogram on March 29, 1935, showing increase of internal hydrocephalus

These medicinal agents included pituitrin (grains II, twice daily), whole pituitary gland extract, thyroid extract (grains $\frac{1}{2}$, three times daily), Collip's diabetogenic pituitary extract, MacCallum-Laughton's duodenal extract, acetylcholine, and atropine. The injection of atropine, however, seemed to produce a violent attack which was difficult to control even with intravenous glucose.

The patient received two courses of non-specific foreign (typhoid vaccine) protein therapy. During the first series, which was given soon after admission, his seizures were arrested for a short period, and for this reason it was thought advisable to repeat this procedure. However, the second course of treatment had little effect on his general condition or blood sugar and did reduce the number of seizures. Blood sugar estimations before, during, and after a chill showed no changes.

Dietary measures were also discouraging. Controlled high and low carbohydrate diets with and without insulin were given a trial. The optimum conditions seemed to exist when he was allowed to eat a regular ward diet, supported at first by occasional and later by regular drinks of sweetened orange juice between meals, particularly when an oncoming attack was expected. For one month an attempt was made to induce ketosis with a ketogenic diet on the presumption that this would stimulate glycolysis; cooperation could be obtained for a high fat ketogenic diet of not more than 1:3 ratio. However, acetone was never obtained in the urine and the condition was unaffected.

As a final measure a two month course of deep roentgen-ray therapy directed to the pancreas was administered. A total of 1500 r were directed in each of two fields without any alteration of the blood sugar or the other symptoms.

(g) *Discharge and Follow-Up* The patient was discharged and transferred to the Montefiore Hospital for convalescent care on April 4, 1935. His course (to March 1936) at this institution has shown no marked changes except that his obesity has increased, the neurological picture has persisted.

COMMENT

The symptoms and signs in this patient were almost entirely neuropsychiatric and included changes in the central, peripheral and vegetative nervous systems as well as in the psyche. Such disturbances are characteristic of most cases of hypoglycemia. The most prominent and constant neurologic manifestations in the case were those referable to diseased striatocerebellar pathways. Throughout the period of observation the patient presented a typical Parkinsonian syndrome, which was progressive in nature, and therefore suggested a primary disease of the basal ganglia. Other significant neurologic changes included a transient attack of peripheral polyneuritis, progressive bilateral nerve deafness, emotional and intellectual deterioration, and progressive internal hydrocephalus.

The diagnosis was complicated by a number of unusual features. The clinical history was not suggestive of hypoglycemia since there was no noticeable relation between the symptoms and the intake of food, the attacks had occurred at any period during the day and despite the ingestion of meals. It is significant that the condition was considered as a neurologic problem in two hospitals. On admission, when the patient was in stupor an intravenous injection of glucose yielded no improvement. Recovery following the intravenous administration of glucose was not noted until about four months after admission. It is therefore evident why the hypoglycemia was not recognized, or even suspected on admission. A similar observation has been reported by Ferner, Soltz, and Haun⁴ in a verified case of adenoma of the pancreas. This observation is difficult to explain.

The fasting venous blood sugar estimations were remarkably low as compared to other reported cases. The general level of the reducing substances varied from 30 to 45 mg per cent and when allowance was made for other reducing substances the least fermentable sugar was estimated as low as 5 mg per cent.

It was also found that there was no strict parallelism between the level of the blood sugar and the severity of the symptoms (figure 1). At certain times the blood sugar values were low without attacks, whereas at other times when the levels were higher convulsions were present. Too, most of the seizures occurred in the afternoons (table 1) despite the fact that the patient ate his lunch. It is possible that the ingestion of food may have overstimulated insulin formation. The ingestion of food did not prevent symptoms of hypoglycemia, a fact contrary to most reports. Most observers state that the intake of food, especially in the form of sweetened orange juice prevents or checks the hypoglycemic attack almost immediately. In our case no method except the intravenous administration of glucose was successful. Even small amounts of glucose by this channel were effective. Glucose by mouth, by rectum or subcutaneously was without result. The effect of fever therapy in this case merits additional reference. During the first course of foreign protein therapy, the patient showed remarkable improvement and convulsive seizures did not occur. At a later period, however, the repetition of this treatment was less effective, in that the hypoglycemic attacks diminished in number but did not disappear entirely as previously. Moreover, blood sugar estimations at this time showed no change, the fasting and other sugar values were the same as on days prior to the institution of foreign protein therapy. Theoretically, if the condition of our patient may be considered as one of hyperinsulinism, the fever therapy may have been effective in reducing the activity of the endogenous insulin. The occurrence of this phenomenon is well known in febrile diabetic patients in whom it is found necessary to increase the maintenance doses of exogenous insulin.

This is probably the first case of hypoglycemia in which progressive internal hydrocephalus has been demonstrated by encephalography. The exact significance of this change must await pathological studies. Other noteworthy alterations during the hypoglycemic seizure were increased salivation, changes in the T-waves of the electrocardiogram, a decrease of blood cholesterol, and a reduction of ocular tension. The latter finding is similarly found in the quite contrary condition of diabetic coma.

The etiology of the hypoglycemia in our case is not clear. Some authors attach importance to the pituitary gland as a causative factor, but the evidence for such an hypothesis is not well established. The only endocrine disturbances manifested in our patient were increase in weight and development of greasiness of the face, and these may be due to disease in the vegetative nervous system. The obesity was probably due to an increase in the caloric intake from the sweetened orange juice given every two hours in order to avoid the hypoglycemic attacks. Diseases of the pancreas, liver and adrenals as the cause of hypoglycemia were probably excluded by exploratory laparotomy and biopsy. However, biopsy of normal tissue from one part of the pancreas or liver, or palpation of the adrenals does not necessarily exclude pathologic lesions in other parts of the explored organs. Furthermore one may also be reminded that it is possible to have abnormal function in the presence of normal morphology. In the final analysis altered function is more significant than altered structure. Numerous instances have been cited where individuals were suffering with hypoglycemia of unknown etiology. These cases are designated as idiopathic, and in most instances the pancreas has been explored and found to be negative.

Finally in our patient, the persistence of the extrapyramidal syndrome raised the question whether the disease of the periventricular nuclei caused both the abnormal movements as well as the hypoglycemia. Theoretically it is possible that disturbances in the sugar metabolism may occur from disease of the glucose regulating center in the brain. As a matter of fact, a case of acute lethargic encephalitis associated with disturbances in sugar metabolism and vegetative functions was recently observed by us. The course, however, in this case was acute and brief, and the disturbances were transient. In the patient with "chronic hypoglycemia" the symptoms and signs of basal ganglia disease were insidious in onset and persistent. From these observations one may infer that disease of the vegetative centers may produce chronic hypoglycemia. On the other hand, one may argue that a persistent hypoglycemia, whatever the cause may be, may produce permanent damage to the brain and therefore produce manifestations of disturbed nerve function. Recent experiments performed on rabbits revealed that convulsions caused by hypoglycemia produced definite anatomic changes in the central nervous system, and the greater the number and the more prolonged the convulsions, the more severe were the lesions.⁵ Our patient had numerous convulsions and encephalograms taken a few months apart revealed a progressive internal hydrocephalus. It is possible that the changes in the brain in this case were caused by the repeated convulsive seizures. On the other hand, it may be claimed that the internal hydrocephalus was the result of primary disease of the brain and that the hypoglycemia which caused the convulsions was secondary.

We are unable to conclude as to which theory is correct. In any case there seems to be a definite relation between disease of the periventricular nuclei and glucose metabolism.

SUMMARY

- 1 A detailed case history of chronic hypoglycemia is described.
- 2 The outstanding features were a persistent Parkinsonian syndrome and evidence of a progressive internal hydrocephalus as shown by several encephalograms.
- 3 Attention is called to the coexistence of manifestations of chronic disease of the periventricular nuclei and the constant hypoglycemic state. The relation between these two is discussed from the standpoint of etiology, but no definite conclusions are drawn.

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UVEO-PAROTID FEVER, WITH CASE REPORT

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UVEO-PAROTID fever or Heerfoidt's disease, is a comparatively rare affection characterized by (1) an iridocyclitis, (2) a bilateral almost painless swelling of the parotid glands, (3) a low grade chronic fever running a course of from several weeks to two or three years and subject to considerable variations, and (4) by the occurrence of irregular constitutional symptoms. The syndrome may occur at any age but is most common in the second and third decades, and is slightly more prevalent in females.

Of frequent, though not constant, occurrence are (1) a prodromal stage, lasting for several weeks or months of general malaise and drowsiness with a tendency to frequent gastrointestinal upsets and abdominal pains, (2) paresthesias and polyneuritis, (3) paralysis of the cranial nerves particularly the seventh, (4) a rash resembling erythema nodosum occurring chiefly on the extensor surfaces of the forearms and legs and extending slightly above the knees and elbows, (5) a polyarthritides, (6) swelling of the cervical lymph nodes and the submaxillary and lacrimal glands, (7) a polyuria without glycosuria, and (8) a long continued dryness of the mouth.

The eye symptoms are quite variable. They may include misty vision with more or less impairment of sight, narrowing of the palpebral fissures, ciliary congestion, sluggish and often irregular or dilated pupils with little or no response to light or accommodation, vitreous opacities, optic neuritis or atrophy, iritis, keratitis, cataract, and glaucoma.

The parotid swellings are usually bilateral and painless. They may be hard or nodular and limited to the pre-auricular area or much more extensive involving all of the salivary tissue. This engorgement usually lasts several weeks or months, but the glands never suppurate.

There seem to be great variations in the order of the appearance and in the severity and duration of symptoms, but the similarity in cases thus far reported unquestionably justifies the classification of a separate clinical entity.

CASE REPORT

History of Present Illness. The patient, a white female, aged 33, was seen by me at her home late in the night of February 14, 1935 for a severe headache and pain in and over the eyes. She also complained of a slight sore throat and aching of the entire body which had begun four or five days previously. The temperature was 102.5° F, and the pulse 110, otherwise the examination was essentially negative. Her suffering was apparently so intense that I administered morphine gr 1/2, hypodermically, which soon gave fair relief. During the next two or three days I received reports to the effect that she was much improved, being able to keep fairly comfortable by the use of aspirin alone. On the eighteenth I was called to see her again, and found that in addition to an exacerbation of the initial symptoms, a distinct redness of the conjunctivae and a photophobia had developed. Two or three days later the patient complained of a blurred or misty vision and of not being able to distinguish objects in the room unless they were brought very close up. Also, she complained of an intense dryness and stickiness of the mouth. At this time there was noticed some degree of swelling on both sides of the face in the regions of the

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parotid glands This swelling was not painful, but was slightly tender on pressure The posterior cervical glands were also enlarged and slightly tender Within the next two days there developed some edema of the upper lids, and the photophobia was more pronounced, also, the pupils were dilated and reacted very poorly to light The temperature continued to range from 100° F to 102° F, and the patient became quite drowsy, being disturbed at intervals with pains about the head During the next few days the swelling of the parotids increased, the eyes became swollen completely closed, and the mental state varied from an intense drowsiness or lethargy to a wandering hallucinatory delirium On February 23 and 24 an eruption appeared on the extremities, extending from approximately the middle of the arms and thighs down to and including the hands and feet, but most pronounced on the forearms and legs and involving chiefly the extensor surfaces The lesions consisted of discrete, ecchymotic, subcuticular nodules, varying in size from about $\frac{1}{4}$ cm to $1\frac{1}{2}$ cm in diameter Two days later, or 16 days from the initial onset of symptoms, the patient was admitted to the Wesley Long Hospital

Family History A husband and two children, ages 12 and 6 years, are living and well Both children, however, were sick for several days with "colds" a week or two before the onset of the patient's present acute illness Neither of her children has had mumps, nor has there been any illness in the home since the patient's attack suggesting contagion Six years ago her husband's sister who had active pulmonary tuberculosis visited in the home for two weeks Otherwise the family history is negative

Personal History The patient sleeps fairly well, her appetite is good, there is no constipation or apparent inability to digest foods Her maximum weight was 145 lbs three years ago, present weight is 137 lbs Menstruation began at the age of 15 and was regular and normal until after the second child was born six years ago Since then it has occurred at five to seven week intervals, the flow is scant and lasts only two or three days There have been two normal pregnancies and no miscarriages

Past History She had measles, mumps, whooping cough, and German measles as a child Her tonsils were removed about 10 years ago Eight years ago she had an operation at which the appendix and one ovary were removed and the gall-bladder drained Six years ago, and about four or five months after the sister-in-law with tuberculosis visited in the home, the patient developed a pleurisy of the left side which lasted several weeks, but has never recurred Moreover, she has had two roentgen-ray studies of the chest since which did not reveal evidence of tuberculosis About two and a half years ago the patient began having headaches, chiefly occipital, and after having her glasses changed several times the headaches improved She also complained of a general malaise, weakness and fatigue Shortly after this she began having attacks of stiffness in the wrists, shoulders, and neck, especially following exposure to drafts at night Soon there developed pains in the chest and lower abdomen, and pains and stiffness in the lower part of the back, in the hips, legs, arms, and joints—especially of the wrists, hands, and ankles Also, she was found to be running a slight fever

On July 16, 1933, the patient called at my office complaining of swollen glands about the neck, and stated that the condition had been developing for a week Her temperature was 102° F, the cervical lymph nodes, both anterior and posterior, were greatly enlarged, and there was slight enlargement of the epitrochlears She was confined to bed for four weeks during which the glandular enlargement gradually diminished without suppurating, but the glands remained definitely larger than normal Also, the temperature ranged lower, but continued to run from normal to 100° F Undulant fever was considered, and upon inquiry it was elicited that a cow from which the family used milk had recently aborted Blood was taken two weeks from the onset of this attack, and again one week later, for agglutination

against *Brucella*, both, however, were negative. The blood Wassermann was negative, and an intradermal tuberculin test was positive. A leukocyte count at this time was 4,500 with a normal differential. Two weeks later the patient was referred to an otolaryngologist who was unable to find any evidence of disease in the throat and sinuses. She was then referred to a dentist who found several diseased teeth which were extracted over a period of several months. The following October (1933) she was admitted to Duke Hospital (Durham) where a very complete study of her condition was made. A summary of their significant findings are as follows: Enlarged cervical and epitrochlear lymph nodes, temperature 100° F, pulse 126, slight tenderness in the sacro-iliac joints, lower abdominal quadrants, and right adnexal region of the pelvis, a negative agglutination test for undulant fever, a positive tuberculin test, a low glucose tolerance (209 mg per cent at 15 hours, and 130 mg per cent at three hours), and a metabolic rate of minus 2 per cent. No diagnosis was made, but an impression of the presence of neurasthenia and, possibly, of a tuberculous infection of the Fallopian tubes was offered. Her course continued practically unchanged for approximately the next 18 months, or until the acute condition herein described developed in February 1935, when she was admitted to the Wesley Long Hospital.

On admission to the hospital the temperature was 101° F, pulse 100, and respirations 22. The heart, lungs, abdomen, and reflexes were apparently normal. In fact, with the exception of the symptoms above described, the physical examination was essentially negative.

Laboratory Findings. Urine. An occasional red blood cell and a few pus cells were found on one occasion, otherwise, negative. Blood. Erythrocytes, 3,420,000, hemoglobin (Sahli), 78 per cent, leukocytes, 16,500 with 82 per cent polymorphonuclears, 14 per cent small lymphocytes, 3 per cent large lymphocytes, and 1 per cent eosinophiles, blood platelets, 258,400, coagulation time, 4½ minutes, bleeding time, 1 min 40 sec. Two blood cultures were negative after five days' incubation, and a culture of material aspirated from several of the subcutaneous nodules was contaminated. Roentgen-ray (Dr E. D. Apple). "Stereo films were made of all sinuses. Both ethmoidoids show cloudiness involving all of the cells, the cell outlines, however, are not completely obscured. The sphenoids also appear slightly clouded. Both antra show evidence of thickened lining membrane, they do not contain fluid. The left frontal is very small and shallow. The right is larger, though still small. They both appear clear."

On the same day of admission Dr. Frank Sharpe saw this patient in consultation with me, and the following day I had Dr. E. Prefontaine (ophthalmologist) see her and take over the care of the head condition. A report of his findings and conclusions is as follows: "The patient was very drowsy. She complained of a marked photophobia and dimness of vision which had existed for about two weeks. There was a fullness of the neck and face similar to that present in mumps, a marked edema and redness of both upper lids, and a skin rash on the forearms and legs. Closer observation revealed the following: chemosis of the conjunctivae, generalized, but most marked on the temporal sides of the corneas, no evident pericorneal injection or corneal deposits, iris clear, but reacting sluggishly to light, and ocular movements normal in all fields. Intra-ocular examination—difficult on account of ptosis and photophobia—revealed media clear and eye grounds normal. No visual test was made. Examination of the nose and para-nasal sinuses revealed a marked bilateral edema and irritation of the nasal mucosa, and a purulent secretion in both nostrils. On transillumination both antra and frontals were moderately dark. The pharynx was dry and granular. There were hard nodular swellings in the regions of both parotids. The sublingual and submaxillary glands were apparently normal. After four days the edema of the lids began to disappear from the nasal side. Chemosis now being localized to the upper temporal region, the edematous lacrimal glands

could be definitely palpated, and, on retracting the upper lids, were visible. Conclusions: Acute ethmoiditis, acute parotitis, acute dacryoadenitis. Also, in considering the history of photophobia and dim vision which were most marked before the patient's admission to the hospital, it is most probable that some ciliary irritation or some neuro-retinitis had existed in spite of the absence of positive findings at the time of examination." Briefly, within three or four days following admission the symptoms began to abate, and after a stay of 11 days she left the hospital much improved and fairly comfortable. It was noticed, however, from the nurses' records that while in the hospital she voided from one to three times every night between 8 p.m. and 6 a.m.

Two weeks after leaving the hospital another examination by the ophthalmologist revealed that the vision had returned to normal, and that there were no synechiae or corneal deposits, or any evidence of optic neuritis or atrophy, also, the nasal condition had entirely cleared up. At this time the rash on the limbs, the swelling of the parotids, and the edema of the orbital tissues had practically disappeared, but there persisted for at least two months a very noticeable narrowing of the palpebral fissures. Also, during this time the patient ran a slight fever almost continually. It seldom rose above 100° F., and seemed to manifest no daily regularity, being highest in the morning about as often as in the afternoon or evening. In addition she suffered frequent attacks of severe abdominal pains, and the neuritis and joint and muscle pains continued to be quite annoying, moreover, the nocturia continued with a frequency of from one to five times every night. After about five months, or during the month of July, all of these symptoms began to abate, and by November had almost entirely disappeared. The fever first began to intermit daily, then at longer intervals, and later was seldom found above normal. Another examination of her chest, including a roentgen-ray study, was made at The Guilford County Tuberculosis Sanatorium on June 20, 1935, by Dr. M. D. Bonner who reported no evidence of tuberculosis. By late 1935 her weight was 137 lbs., the hemoglobin (Sahli) 76 per cent, and the cell counts normal. A number of urine examinations, including two cultures for tubercle bacilli, have been made with only normal findings. Also, another agglutination test for undulant fever was negative. It seems that in spite of this prolonged illness with fever, the patient has maintained her weight and energies remarkably well, and the blood picture has remained practically normal. Incidentally, it may be of interest to note that she became pregnant in July 1935, her last pregnancy having been more than six years before, and she denies having ever used contraceptive precautions.*

DISCUSSION

Heerfordt,¹ whose name the disease now bears, was the first to recognize and describe this syndrome. In 1909 he reported three cases observed by him in the city hospital at Copenhagen, and discussed two others with similar symptoms from the literature,—one reported by Daireaux and Pechin in 1899, and the other by Collomb in 1903. Merrill and Oaks,² in reporting a case in 1931, reviewed the literature up to that date and tabulated an analysis of 29 previously recorded cases. Later Garland and Thompson³ gave a still more comprehensive review of the subject, and, more recently, Savin⁴ has presented a most excellent analysis of 66 published cases and added one of his own. Reports of at least seven others⁵ have appeared since Savin's publication, making a total of approximately 74 recorded cases. It is interesting to note that most of the existing

* Since this article was submitted for publication the patient's pregnancy progressed normally to full term. The patient had a normal labor and delivery in February 1936, and in September 1936, reported herself free from fever and in good health.

reports have come from Scandinavia, Germany, and Great Britain, while only six have appeared in American literature. The condition is probably more common than is usually suspected, but is rare enough not to be readily recognized.

Etiology The question of etiology in this disease is very much in controversy, moreover, there is a great diversity of opinion among the authors of reported cases concerning this point. Heerfordt¹ thought his cases were atypical mumps. Fuchs⁶ was of the opinion that uveo-parotid fever could not be definitely separated from Mikulicz's disease, and Hamburger and Schaffer⁷ thought it was a variety of the Mikulicz syndrome. Mohr⁸ ascribed the lesions to syphilis. Viner,⁹ Adams,¹⁰ and MacKay¹¹ thought infections of the mouth were responsible for the condition. Ramsay¹² classed it as a deficiency disease. Parker¹³ considered it to be an infective multiple neuritis with lesions in other tissues (parotid, uvea, skin, etc.). Schall,¹⁴ Garland and Thompson,³ Ulthoff,¹⁵ Roenne,¹⁶ Gjessing,¹⁷ Cavara,¹⁸ and others think the condition is caused by tuberculosis of a particularly fibrosing and noncaseating type—and there is considerable, though not altogether incontrovertible, evidence in support of this view. In fact, microscopically, the histological reactions of the tissues involved are apparently identical with those produced by tuberculosis. Moreover, McCurry¹⁹ actually demonstrated the tubercle bacilli in biopsy sections from both parotid glands of a patient (case 2) presenting the uveo-parotid syndrome. And, of the five patients who have died, tuberculosis was demonstrated in four at autopsy, the fifth was not examined. At least, in the cases thus far reported, there has been an exceedingly high incidence of associated tuberculosis, suggesting very strongly a probable etiologic relationship. Merrill and Oaks² attribute this disease to a "specific virus or bacterium as yet undetermined", while Cohen and Rabinowitz⁵ think it is an infective-allergic condition caused by "an organism, as yet not isolated, which produces a low grade infection in a sensitized individual". In the opinion of the author, the weight of evidence, both from reported cases and from the clinical course and picture of the case observed, suggests very strongly that the condition is rheumatic in nature—thus, its protean manifestations.

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AMEBIC ABSCESS OF THE LIVER, REPORT OF A CASE WITHOUT PREVIOUS MANIFESTATIONS OF AMEBIASIS, OPERATION AND RECOVERY *

By HAROLD L GOLDBURGH, M D, *Philadelphia, Pennsylvania*

VARIOUS authorities differ as to the prevalence of amebiasis in countries other than the tropical regions. It is claimed that it occurs in the temperate climate more frequently than is generally believed. Craig's¹ opinion that between 5 and 10 per cent of the American population harbor this infestation is based on his collected statistics of 49,336 persons examined, 11.6 per cent having been found positively infected. Sir Leonard Rogers,² quoting C. Dobell, stated that between 7 and 10 per cent of the people of North England were carriers of the *Endameba histolytica* during the Great War. In 1934 Wenrich, Stabler and Annett,³ of the University of Pennsylvania, examined 1,060 freshmen students at a professional school in Philadelphia and found that 4.1 per cent harbored the *Endameba histolytica*.

In Philadelphia prior to the Chicago epidemic of 1933 amebiasis was a sporadic disease. Between January 1926 and November 1935, among 232,100 admissions to the Philadelphia General Hospital, there was one proved case of amebic dysentery, admitted in September 1930 to the service of Dr. Russel Boles. At the Jefferson Hospital during the same period, among approximately 120,000

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From the service of Dr. Samuel A. Lowenberg, Philadelphia General Hospital.

admissions, there were six cases of amebic dysentery. All followed the Chicago epidemic, three occurring in the latter part of 1933 and three in 1934. Up to November 1935 the Bureau of Health of Philadelphia⁴ had recorded 43 cases of proved amebiasis all of which had likewise occurred subsequent to August 1933 when the segregation of the dysentery cases was first started.

The most frequent complication of amebiasis and amebic dysentery is abscess of the liver. It is frequently undiagnosed before death especially in temperate climates where amebic infection, until recently, was little understood and was



FIG 1 *Endameba histolytica* Vegetative form discovered in the abscess cavity $\times 2024$

regarded by most of the profession as a tropical disease. Ochsner and Bakey⁵ have reported on 4,484 cases of amebic abscess of the liver collected from the literature. According to some investigators amebic abscess of the liver is observed in from 2 to 20 per cent of those infected but living and in from 15 to 59 per cent of the autopsied cases of this disease. Brown⁶ reported 22 cases of hepatic involvement from the records of 834 cases of amebiasis at the Mayo Clinic. Of these 16 were proved cases of hepatic abscess, approximating 2 per cent.

At the Philadelphia General Hospital during the last 10 years, among the 232 100 admissions and 24,000 autopsies, there were five cases of proved amebic abscess of the liver. Three cases were diagnosed clinically. The first was operated on by the late Dr Hiram Loux in 1925. The second was the case which is the subject of this report, occurring in October 1935. The third was admitted later in 1935 and was operated on by Dr Mitchel P Warmuth. The remaining two were diagnosed at autopsy. At the Jefferson Hospital during the last 10 years there has been but one case of clinically proved amebic abscess of the liver, admitted on July 31, 1933, to the service of Dr Henry K Mohler and operated upon by Dr Thomas Shallow. This was the only case recorded in this hospital although approximately 3,000 autopsies were performed within this decade. If amebiasis is, or has been, prevalent in Philadelphia either our diagnostic acumen, or our laboratory methods, or our records are at fault.

Various investigators claim that from 50 to 90 per cent of the cases of amebiasis have symptoms not usually dysenteric but mild and attributed to some other factor. It is the latent infections in the carriers and the amebic cysts that are not recognized and become potential dangers both to the host and to the community.

It must be remembered that abscess of the liver may be the first symptom of amebiasis. Ochsner and Bakey⁶ claim that they have found a relatively large number of cases of amebic hepatitis without a history of diarrhea. An explanation may be that slight amebic infection of the bowel, limited to the right half of the colon is less likely to produce diarrhea. On the other hand, Strong⁷ has found a history of dysentery in 60 to 90 per cent of the cases of liver abscess. Three of the four proved cases recently reported by Freund⁸ failed to present any evidence of previous gastrointestinal symptoms. Rogers,⁹ in 1930, reported that in 20 per cent of the cases of amebic abscess of the liver coming to autopsy in Calcutta there had been no history of dysentery. However, he found amebic ulcers, limited to the cecum and ascending colon, in 77 per cent of such cases and ulcer scars in 20 per cent more—a total of 97 per cent which yielded pathological evidence of intestinal amebiasis.

Because of the apparent rarity of amebic abscess of the liver in this climate and because of its occurrence in a patient without previous history of amebic dysentery, the report of the following case, diagnosed following operation, should be of interest.

CASE REPORT

History. J. L., white, 58, Polish, a tanner unemployed for five years, was admitted to the Philadelphia General Hospital on September 16, 1935. Because of the language difficulty and the ignorance of the patient a good history was not obtainable. He claimed that he had been well until September 9, 1935 when he noticed a sudden onset of severe pains in the right upper abdomen, griping in character, coming on every hour or hour and one-half and lasting for 15 minutes. The pains had no relationship to food and were not associated with nausea, vomiting or diarrhea. He had persistent hiccoughing. There were no symptoms referable to the cardiac or respiratory systems. He was chilly, had fever, and felt quite drowsy.

In his past medical history he did not remember having had any childhood diseases or of having had any previous illness, hospitalization or operation. He had never been jaundiced. He had never had dysentery or blood in his stools but contrarily had been constipated. He had not traveled outside of Philadelphia. There was no history of his having come in contact with carriers.

After the operation and after a month of repeated questioning of the family we were able to procure some additional information from the patient's daughter. She stated that for a period of 15 years her father had had pains in his right upper abdomen with heartburn independent of the taking of food. There were attacks of abdominal cramps, without diarrhea, coming on twice a week and lasting 24 hours, associated with chilly sensations. These pains were relieved in one hour by taking a tablespoonful of coal oil with sugar. Upon further investigation it was learned that his son-in-law, who lived in the same house, had been treated at the Jefferson Hospital since September 1933 for a bloody diarrhea. Repeated stool examinations failed to reveal the presence of the ameba. As far as we could ascertain, no other member of the household was affected.

Examination The patient was a slightly emaciated and dehydrated adult male who appeared distressed. The conjunctivae were not icteroid. The nose, mouth and throat were negative. The heart seemed normal. The systolic blood pressure was 115 and the diastolic pressure was 85 mm of Hg. The chest was emphysematous. The bases of the lungs were hyperresonant without any apparent fixation of the diaphragm. The abdomen revealed moderate fullness in the epigastrium over which area there were pains and tenderness which were made worse upon breathing. The upper limit of the liver dullness commenced in the fifth intercostal space anteriorly in the mid-clavicular line and extended 6 centimeters below the costal border. The lower edge of the liver could not be palpated because of the voluntary rigidity of the upper abdomen. The lower abdominal wall was relaxed. The spleen was not palpable, nor enlarged on percussion. There were no signs of fluid in the abdominal cavity. Rectal examination revealed normal sphincter control and no masses. The prostate was slightly enlarged. The examination of the skin and of the nervous systems was negative.

The temperature ranged between 100.4 and 102.1 degrees F. The pulse rate was 94 to 100 per minute and respirations were 30 per minute. The first blood count was Hb 14 gm, rbc 3,840,000, wbc 16,000 per cu mm of which 96 per cent were polymorphonuclear. Of the latter 26 per cent were segmented and 70 per cent were stab forms. The lymphocytes constituted 2 per cent and the monocytes 2 per cent. There were no eosinophiles. The urine showed traces of albumin and was negative for bile. The Wassermann was negative. The urea was 10 mg and the sugar was 90 mg per 100 c.c. of blood. The icterus index was 10.

In the absence of a history of dysentery and because of the sudden onset of the distressing symptoms and signs suggestive of acute suppurative cholecystitis with secondary hepatitis, the patient was operated upon by Dr. Patrick McCarthy on September 18, 1935.

Upon entering the peritoneal cavity he found the gall-bladder and spleen to be normal. The left lobe of the liver was much enlarged and extended down to the umbilicus. The right lobe showed nutmeg-like surface markings and across its lower border extended a deep transverse scar about three-quarters of one inch deep which gave it the appearance of a luetic liver. Further palpation revealed another such scar running vertically and situated at the dome of the right lobe. Towards the middle of the right lobe an area protruded somewhat above the general liver surface which was bluish-gray in appearance. This area was found to be soft and fluctuant. Aspiration of the abscess yielded a thick, whitish pus. A cannula and suction drained off 10 ounces of a thick, creamy, slightly brownish pus. A 24 gauge catheter was introduced in the abscess cavity and sutured in place to the liver. The area about the liver opening was packed with iodoform gauze and the peritoneal cavity was closed.

The pus was immediately examined by Dr Jefferson Clark who found the *Endameba histolytica*. The amebae were of large size with faintly visible nuclei and distinct refractile ectoplasm. They exhibited marked motility and contained vacuoles and occasional red blood cells. The cultures made from the pus revealed *Bacillus coli*.

Dr R. P. Custer's examination of the liver tissue removed at the time of the operation revealed a marked chronic proliferative peri-portal hepatitis.

Two days following the operation the distressing symptoms subsided. The temperature returned to normal where it remained. The drain was removed in seven days after which the incision healed and convalescence was uneventful. The patient was able to resume a full diet.

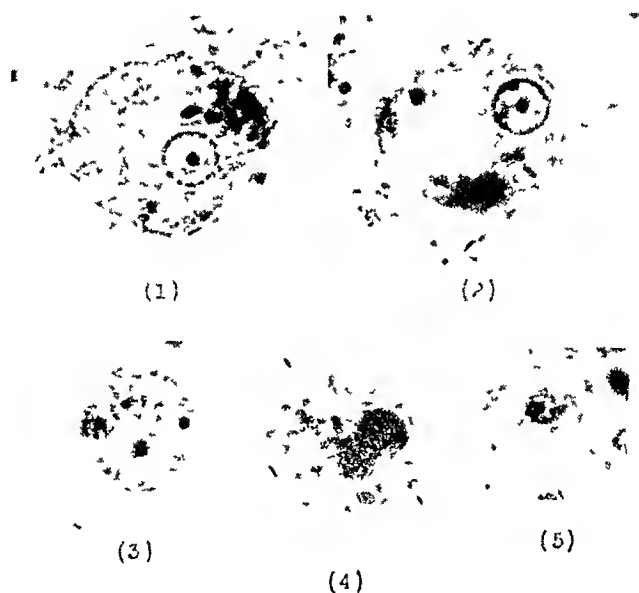


FIG 2 (1 and 2) *Endameba histolytica* Vegetative forms removed from the abscess cavity of the patient. For comparison (3) *Endameba histolytica* Cyst (4) *Endameba coli* Vegetative form (5) *Endameba coli* Cyst form $\times 2024$

After his return to the medical service, the first week in October, further studies were inaugurated. The bromsulphthalein test showed no retention beyond 30 minutes. The gastric analysis was normal. Ten stool examinations done while in the hospital were negative for ameba and for cysts. Duodenal drainage did not reveal the presence of the ameba. The Craig complement fixation test was not performed.

The proctoscopic examination revealed that the anus showed a fissure at the posterior commissure. There was a nest of internal hemorrhoids. The lower 10 centimeters of the bowel were normal showing no evidence of ulceration.

A roentgen-ray of the chest was normal. The diaphragm was not altered in function or position. Roentgenographic study of the colon revealed that barium passed uninterruptedly from the rectum to the cecum. There was a marked reduplication of both flexures and ptosis of the transverse colon which lay over the first sacral segment. Numerous annular radiolucent shadows were seen throughout which

were caused by intestinal gas. There was marked irregularity about the cecum but no demonstrable irritability. The appearance was suggestive of some inflammatory processes involving the cecum.

The patient was discharged as clinically relieved on November 21, 1935.



FIG 3 Roentgen-ray of the colon. Note the marked irregularity about the outer edge of the cecum and the ascending colon suggesting an inflammatory process.

TREATMENT

Upon the patient's return to the medical ward amebicidal therapy was instituted. It is interesting to note that, because of abdominal cramps over a period of 15 years, he had been accustomed to take a tablespoonful of coal oil by mouth twice a week and had obtained relief. Kerosine has been used for amebiasis.

Every suspected or proved case of amebic abscess of the liver should be given the advantage of a course of emetine therapy before any other procedure is used unless there is an apparent surgical complication. However, Reed¹⁰ believes

that intensive emetine treatment should be avoided before operation because of the possible harmful effect on the myocardium

If the symptoms and signs persist after amebicidal therapy then surgery is indicated. Although there may be multiple amebic abscesses of the liver, the majority are solitary and in the right lobe of the liver, and are sterile. In Ochsner and Bakey's⁵ series of 386 collected cases where smears and cultures were made from the pus of amebic abscesses of the liver, 328, or 83.9 per cent, were found to be sterile. In their own 46 cases, 41, or 89 per cent, were free from bacteria. The consensus of opinion is that closed drainage is the method of choice. It is based on the experience of Rogers² who has shown that the mortality rate of open drainage was as high as 56.8 per cent while in closed drainage the rate decreased to 14 per cent. In Ochsner and Bakey's⁵ 4,035 collected cases, following open drainage there were 1,908 deaths, a mortality rate of 47.2 per cent. In the 459 cases treated by closed drainage and the administration of appropriate doses of emetine they found 32 deaths, or a mortality rate of 6.9 per cent.

When smears of the abscess contents examined at the time of aspiration show the presence of a large number of microorganisms, or when fluid re-accumulates in spite of repeated aspirations, and when there are indications of surgical complications, such as beginning perforation, then open drainage is to be preferred. In all other cases the consensus of opinion is that open drainage is contraindicated.

Immediately after the operation intramuscular injections of emetine hydrochloride should be given in doses of 1 grain daily, not exceeding 10 milligrams per kilogram of body weight. The average adult should not receive more than 10 grains.

Amebicides as acetarsone, carbarsone, tryparsol, chiniofon and vioform are safer and more efficient in the treatment of amebic dysentery. Leake¹¹ believes that they should not be used in amebic hepatitis and liver abscess because they may be toxic to the liver.

SUMMARY

If amebiasis is present in between 5 and 10 per cent of the American population, it is of interest that the records of the Philadelphia General and Jefferson Hospitals contain so few diagnosed cases. Since the Chicago epidemic more cases are being discovered. In Philadelphia amebic liver abscess is still rare. At the Jefferson Hospital during the last decade there was one case among approximately 120,000 admissions and 3,000 autopsies. During the same period at the Philadelphia General Hospital among approximately 232,000 admissions and 24,000 autopsies there were five proved cases. Three, including this case, were discovered clinically and two at autopsy.

It must be remembered that in a high percentage of cases the first symptom of amebiasis may be an abscess of the liver, as occurred in this case. The time elapsing between the infestation and the appearance of the liver abscess may vary from a few months to many years. The symptoms and signs may simulate any surgical liver condition. There may be moderate leukocytosis but no eosinophilia. In the absence of a history of amebic dysentery the primary lesions in the majority of instances can be located in the cecum and ascending colon which

would produce no diarrhea. The roentgen-ray examination by a contrast enema will reveal the local lesions as was found in this case.

In the absence of myocarditis every suspected or proved case should receive emetine therapy before any surgical procedure. Closed drainage is the method of choice. Open drainage without irrigation is indicated when there is beginning perforation or a mixed infection or re-accumulation after repeated aspirations and emetine therapy. It is the consensus of opinion that the arsenicals and oxyquinoline groups of drugs should not be used in the presence of liver damage.

The author wishes to acknowledge due thanks to Dr. Jefferson Clark, Director of Laboratories of the Philadelphia General Hospital, for his extreme cooperation.

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EDITORIAL

SEQUELAE OF ASPHYXIA DURING NITROUS OXIDE ANESTHESIA

NITROUS oxide-oxygen anesthesia is generally considered the safest of the general anesthetics. This belief is founded on a number of statistical studies of the anesthetic deaths occurring in very large series of general anesthetics from many countries. It is no doubt correct. Nevertheless most experienced anesthetists stress the need of particular watchfulness in the administration of nitrous oxide and the necessity of experience in its use before prolonged periods of deep surgical anesthesia are attempted.

To many internists who have had occasion to watch patients through nitrous oxide-oxygen anesthetics the reputed safety of this anesthetic must seem remarkable. Figures indicating that it causes death only once in one to five million cases are scarcely credible in the face of the obvious risks entailed in the state of semi-asphyxiation evidenced by these patients. Often this incredulity is heightened by a personal memory of one or more unreported fatalities attributable to gas anesthesia. The recent appearance of a very interesting paper by Courville¹ reporting 13 cases of nervous sequelae after nitrous oxide-oxygen anesthesia will probably result—if medical history repeats itself—in numerous further reports of similar instances and perhaps temporarily in an unreasonable degree of apprehension concerning the use of this anesthetic.

In general in the cases described by Courville nitrous oxide-oxygen anesthesia was followed by prolonged coma or stupor, by delirious states, by convulsions, muscular rigidity, extensor spasms, paralyses, etc. Nine of the 13 cases died after an interval of from 40 hours to 26 days. Four recovered, two completely and two with serious residual neurologic and mental defects. Examination of the brains in the fatal cases was carried out with great thoroughness. The macroscopic changes were minimal but histo-pathological studies showed very extensive alterations chiefly in the cortex and in the lenticular nuclei. The most striking of these lesions were areas of patchy necrosis of the superficial, intermediate or deep cortical layers. Courville considers the cerebral lesions highly characteristic of the effects of cerebral anoxemia as described in experimental animals by Gildea and Cobb,² and others.

While it is generally conceded that nitrous oxide possesses specific narcotic properties, experience has shown that for full surgical anesthesia it is necessary to give gas oxygen mixtures which produce a definite anoxemia. The unconsciousness of deep nitrous oxide-oxygen anesthesia is in part due

¹ COURVILLE, C. B. Asphyxia as a consequence of nitrous oxide anesthesia, *Medicine*, 1936, **15**, 129-247.

² GILDEA, E. F. and COBB, S. The effects of anemia on the cerebral cortex of the cat, *Arch. Neurol. and Psychiat.*, 1930, **24**, 876-903.

to the nitrous oxide and in part to asphyxiation. In the induction of anesthesia many anesthetists use pure nitrous oxide and then change rapidly to a mixture containing approximately 90 to 93 per cent nitrous oxide with 10 to 7 per cent of oxygen for the maintenance of anesthesia. It is of interest to note that Henderson³ in discussing progressive anoxemia classified as the third stage that in which the atmosphere contains between 10 and 6 per cent of oxygen. Concerning the symptoms he states "The subject loses the ability to perform any vigorous muscular movements. Bewilderment and loss of consciousness follow, either with fainting or in a rigid glassy-eyed coma. If revived the subject may have no recollection of this stage. When the oxygen is diminished below 6 per cent, respiration consists of gasps. Convulsive movements may occur. Then the breathing stops but the heart continues to beat for 6 to 8 minutes. Then death."

It is quite apparent therefore that the oxygen percentage in the usual anesthetic mixture is quite low enough to produce definite symptoms of anoxemia and that there is a very narrow margin of safety between the usual percentage and that which would not maintain life.

The mixture inhaled is moreover only one factor in the problem of ensuring an adequate oxygen supply to the cells of the vital centers. Obstruction of the airways, inadequate respiratory movements, pulmonary lesions interfering with absorption, increased circulation time, low hemoglobin content of the blood, factors decreasing the dissociation rate of oxyhemoglobin or the intracellular utilization of oxygen and finally muscular exertion, which greatly increases the body's oxygen needs, may all bring about severe tissue anoxia even in the presence of an adequate oxygen percentage in the gas mixture inhaled. It is obvious, therefore, that the anesthetist has many things to consider in adjusting the mixture to the needs of the individual patient and in combating such impediments to the ultimate tissue use of oxygen as he can alter with the means at his disposal. As to his judgment of the efficiency of the oxygen supply he must be guided by skin and mucous membrane cyanosis, the color of shed blood, and even more importantly by such signs of cerebral asphyxia as forced expiratory movements, clonic and tonic muscular contractions and widely dilated pupils.

It seems strange that as yet we have very few observations on human beings as to the degree of oxygen unsaturation of arterial blood during nitrous oxide-oxygen anesthesia. Those published by Raginsky and Bourne⁴ suggest that there are extraordinary variations in this respect within the range of uncomplicated anesthesia. These authors in a study of 14 cases found that towards the latter part of anesthetics, varying in duration from 10 to 30 minutes, the arterial blood showed oxygen unsaturation varying between 53.3 and 51.1 per cent. Since the mixture administered contained approximately 20 per cent of oxygen, instead of the more usual

³ HENDERSON, Y., and HAGGARD, H. W. Noxious gases, 1927, Chemical Catalogue Co., New York, p. 98.

⁴ RAGINSKY, B. B., and BOURNE, W. Cyanosis in nitrous oxide oxygen anaesthesia in man, Canadian Med. Assoc. J., 1934, xxv, 518-521.

7 to 10 per cent, the extreme degrees of unsaturation encountered are all the more astonishing. There is real need of more extensive investigation of this subject.

If, in a patient under nitrous oxide-oxygen anesthesia, breathing stops temporarily or there is circulatory failure, a period of intense tissue anoxia will be superimposed upon a preceding period of relative asphyxia. It is in such cases especially that cerebral damage may be sustained which will be manifested after resuscitation by the sequelae which Courville has described. In experimental animals with artificially induced cerebral anemia 2 to 15 minutes of anoxemia have been found to cause in most instances irreparable changes in the cerebral cortex and medulla.

In Courville's nine fatal cases of residual coma and convulsions following nitrous oxide-oxygen anesthesia there were six in which during the anesthesia periods of respiratory failure had occurred and in four of these six cardiac failure had also been noted.

In one of these six cases, however, the duration of the anesthesia was brief, "only a few minutes" and the period of cardiorespiratory failure lasted only 4 to 5 minutes, yet this case developed coma, convulsions, extensor rigidity and irregular breathing and died on the fourth day. Moreover, there were three fatal cases in which the period of anesthesia was neither unusually long nor marked by any striking evidences of distress. Such instances suggest a factor of individual susceptibility and this possibility is enhanced by consideration of the many instances of all varieties of severe asphyxia which recover with no apparent residual defects.

Courville's contribution to the toxicology of nitrous oxide-oxygen should arouse interest in a more careful study by modern methods of the effects of this anesthetic upon internal respiration.

REVIEWS

Clinical Heart Disease By SAMUEL A. LEVINE, M.D., F.A.C.P., Assistant Professor of Medicine, Harvard Medical School 445 pages, 97 illustrations W. B. Saunders Co., Philadelphia 1936 Price, \$5.50

This volume has been written primarily for the general practitioner. It stresses bedside and clinical observations. It is especially valuable in that it presents many useful clinical points, derived from the rich experience and accurate observations of the author, not ordinarily found in more pretentious volumes. At times the author is apt to theorize a bit, but it is clearly stated when he is so doing.

There are chapters on the important etiological types of heart disease including a better chapter on functional heart disease than the reviewer has seen in any similar book, chapters on paroxysmal rapid heart action, prognosis, and treatment. Acute cardiovascular emergencies, the clinical significance of the systolic murmur, the patient with heart disease as a surgical or obstetrical risk are discussed in chapters that are excellent and of great practical importance. Chapter XX presents in 113 pages all the practitioner needs to know about electrocardiography.

The style is pleasant and readable, to the point but not too concise. The book is highly recommended.

W. S. L., JR.

The Specificity of Serological Reactions By KARL LANDSTEINER, M.D., The Rockefeller Institute for Medical Research, N. Y. 178 pages Charles C. Thomas, Springfield and Baltimore 1936 Price, \$4.00

Over the course of some years, as the result of the researches of a number of investigators, our conception of the antigen has been considerably modified, and, with this, our ideas about the specificity of the antigen-antibody reaction. A critical review of this work is, therefore, not unneeded. The present book is essentially a translation of the German edition with such alterations and additions as were found necessary to bring it up-to-date. After a short introductory chapter, devoted largely to a clarification of the meaning of specificity, there follows a discussion of the serological specificity of proteins. Next the specificity of cellular antigens is considered and then that of the various antibodies. But the very heart of the work is to be found in the last two chapters, where are presented the investigations on artificial conjugated antigens, so largely carried out by Dr. Landsteiner and his collaborators, and on the chemistry of the specific cell substances—carbohydrates and lipoids. Well organized, clear and concise, with an extensive bibliography, this book presents an excellent review of the subject. Though intended primarily for specialists in the field of immunology, it is not too technical for others who may be interested in this branch of science.

F. W. H.

The Principles and Practice of Medicine Designed for the Use of Practitioners and Students of Medicine. Originally written by the late SIR WILLIAM OSLER, Bt., M.D., F.R.S. Twelfth Edition, Revision by THOMAS MCCRAE, M.D. 1196 pages D. Appleton-Century Co., Inc., New York and London 1935 Price, \$8.50

During the past 10 years, this textbook has not been seen in student hands as often as newer, but possibly less valuable works. This may be due to the infrequency of editions, the present one being only the second since 1925. It is indeed a pleasure

to examine this edition, which has been entirely reset in a type that is distinctly easier to read, as the revisor notes

The preface states, "There are changes and additions in practically every part of the book, perhaps more especially in the discussion of diagnosis and treatment. Certain sections are new or have been materially altered." These changes have been made, however, and the new material added, without sacrificing any of the clearness, simplicity, or completeness of the old text. The original style has been preserved, as well as most of the familiar expressions, while the old and new material is blended smoothly.

It is certainly to the student's advantage to study a text whose original manuscript and subsequent revisions have been in the hands of only two persons. Some recent texts suffer, in contrast, from their multiple authorship. The present volume is striking in its uniformity of style and quality and its conservative modernness.

T N C

An Index of Differential Diagnosis of Main Symptoms. By various writers, Edited by HERBERT FRENCH, CVO, CBE, MA, MD, FRCP. 5th Edition. xii + 1145 pages. Wm Wood and Co, Baltimore. 1936. Price, \$16.00.

This is the most recent edition of a well-known work, first published in 1912 as a companion volume to the publishers' "Index of Treatment." With "An Index of Prognosis, and End Results of Treatment," edited by P. Rendle Short (*Ann Int Med*, 1933, vii, 677-678), it makes up a three volume set, although a different style of binding prevents uniformity of appearance.

The text consists of 925 pages, in which symptoms are listed in alphabetical order. Following each symptom is a discussion of the differential diagnosis of those conditions in which it may be observed, with a fairly complete description of each disease under its most important symptom or physical sign. The index of the book (pages 927 to 1145) is very complete, and must be used if satisfactory results are to be obtained, as the general alphabetical arrangement is incomplete and not cross-indexed.

On the whole, "An Index of Differential Diagnosis" is well written, interesting in style and readable. There are a large number of differential diagnostic tables. The book is fully and beautifully illustrated, having 742 illustrations, of which 196 are colored. Many temperature charts are also included, which, with the illustrations and differential tables, should be very useful for instruction of students.

Unfortunately, as with any work of multiple authorship, there is a tendency toward unevenness of quality. For example, in the long article on jaundice (pages 395 to 416) there is no mention of hemolytic jaundice as such, the different types of hemolytic jaundice being classified under other headings. Thus, the jaundice of malaria is classified with that due to acute fevers and infections, while icterus neonatorum, acholuric jaundice (congenital hemolytic), and paroxysmal hemoglobinuria are placed under "Jaundice Due to Unclassified Causes." The Van den Bergh reaction is poorly described, and the indirect reaction and quantitative estimation of serum bilirubin are not mentioned. Jaundice from cinchophen is not described.

Among other defects are the failure to list lymphogranuloma inguinale as a cause of swelling of inguinal lymph nodes and, in the differential diagnosis of coma, the omission of methyl alcohol or methyl salicylate poisoning. In the section on edema, the effect of depletion of blood plasma protein is not mentioned. In discussing typhus fever, the statement is made that "there is no known serum test for this disease" (p. 681), nor does the Weil-Felix reaction appear in the index.

In spite of these and other faults, the work should prove a very helpful one. Most of the articles are up-to-date and comprehensive. It is almost certainly the most useful of the three "Index" volumes offered by the publisher.

T N C

Human Pathology A Textbook By HOWARD T KARSNER, M D, Professor of Pathology, Western Reserve University Fourth Edition, Revised 1013 pages, 17 X 23.5 cm J B Lippincott Company, Philadelphia 1935 Price, \$10.00

This textbook appeared in its first edition in 1926. Since that time it has been periodically reedited and revised to reflect the continuance of productive effort and accomplishment that the last decade has brought about. The teacher and author, who sets for himself the task of compiling a textbook for students' use, has a multiple problem on his hands. The book must be clear, complete but concise, and must necessarily evaluate, judiciously, the subjects discussed. He further obligates himself, to some degree, to keep the subject matter abreast of the times. Karsner has attempted to fulfill these prerequisites.

The book is divided into two parts, 428 pages being devoted to a consideration of general pathology and 585 pages to pathologic manifestations in the various systems. This arrangement is consistent with the method of teaching pathology in the majority of medical schools. The opening chapter deals with the general phenomena of disease and leads through the more simple processes of pigmentation, degeneration and vascular disturbance to the more complicated subjects of inflammation and neoplasms. Under physical causes of disease the effects on tissue of irradiation are emphasized over previous editions because of the more widespread use of x-ray and radium in the treatment of malignant disease. There are two additions under infectious granuloma that were not present in the earlier editions. These are tularemia and lymphogranuloma inguinale. The chapter on tumors has been almost completely rewritten, without change in the classification. There are also noteworthy changes in the chapters on the hematopoietic system and ductless glands. This has necessitated minor changes in the discussions on tumors in the various systems.

There is some consideration given to the virus diseases as they affect the central nervous system, but no specific mention of lymphocytic choriomeningitis is made. The so-called Rickettsial diseases, typhus, spotted fever, tick fever, are not listed in the index. These are of especial interest in certain localities.

The outline at the beginning of each chapter is especially helpful to the student. The illustrations are well selected and for the most part original. Many are reproduced from drawings. This often exaggerates detail and adds to the clarity of the reproduction. The references are well selected, mostly in English and easily accessible in alphabetical order at the end of each chapter. There are more than 300 new references in this new fourth edition.

The book is primarily a text for students and in this it well fulfills its purpose and further it offers the average practitioner a ready and easily accessible source of information on pathology.

C G W

COLLEGE NEWS NOTES

LIFE MEMBERSHIP

Some years ago the Board of Regents of the American College of Physicians, believing a sound financial foundation to be one of the best guarantees of insuring the stability and perpetuity of the College, provided for the building up of an Endowment Fund, "the principal of which shall be held intact and invested in securities approved by the Board of Regents, while the income shall be available for carrying out the purposes of the organization." This Endowment Fund has been built up primarily through Life Membership Fees, the income from which has materially helped in carrying on the work of the College, especially the promotion of scholarships, fellowships and awards, and may help materially in the furnishing of the new College Headquarters.

The Life Membership Fee, ranging from a minimum of \$100.00 to a maximum of \$300.00, plus the original Initiation Fee, depending upon the age of the member at the time Life Membership is taken out, entitles each Fellow or Master to permanent privileges of membership, to the benefits of the Annual Sessions and to the official publications of the College, including the Directory and the *ANNALS OF INTERNAL MEDICINE*. They receive an appropriate Life Membership Certificate, as illustrated in the Directory of the College, and their names are added to the permanent roll of contributors to the College Endowment Fund. Life Members are *active members for life*.

The plan affords the member an opportunity of paying his full dues during his productive years, while his income is greatest, thus avoiding the burden of dues later in life. The plan is one that provides a means for underwriting dues years in advance, but of receiving the premium of active membership throughout one's entire life. A member pays no more for Life Membership than he would pay for ordinary active membership to sixty-five years of age, without active membership thereafter, yet he receives active membership not only until sixty-five, but for the balance of his life. Many members can readily afford Life Membership during their active, productive years, but, with changing conditions or ill health, find annual dues a burden in later life.

The Life Membership plan of the College is bound to be a successful one because it is two-sided: it is good for the member and it is good for the College. It protects the individual's membership for life, it establishes an Endowment Fund for the College, which must be kept intact, the income only to be used for current needs.

Dr. R. L. Leak, Superintendent of the Connecticut State Hospital, Middletown, Conn., has become a Life Member of the College under date of November 25, 1936.

COLLEGE LIBRARY

With the acquisition of an appropriate headquarters for the American College of Physicians with adequate facilities for housing more appropriately the Library of books written by members of the College, there has been an impetus given to the donation of books by the authors. We are gratified to acknowledge receipt of the following gifts by the authors:

Books

Dr. Wyndham B. Blanton (Fellow), Richmond, Va.—autographed books (1) "Medicine in Virginia in the Seventeenth Century", (2) "Medicine in Vir-

- gimia in the Eighteenth Century", (3) "Medicine in Virginia in the Nineteenth Century",
- Dr William B Castle (Fellow) and Dr George R Minot (Fellow), Boston, Mass — 1 autographed book, "Pathological Physiology and Clinical Description of the Anemias",
- Dr Jacob Gutman (Fellow), Brooklyn, N Y — 1 copy, Eighth Supplement to "New Modern Drugs",
- Dr Samuel A Levine (Fellow), Boston, Mass — 1 autographed book, "Clinical Heart Disease",
- Dr Robert L Levy (Fellow), New York, N Y — 1 book, "Diseases of the Coronary Arteries and Cardiac Pain",
- Dr Jonathan C Meakins (Fellow), Montreal, Que — 1 book, "The Practice of Medicine",
- Dr William C Menninger (Fellow), Topeka, Kan — 1 autographed book, "Juvenile Paresis",
- Dr Martin E Rehfuss (Fellow), Philadelphia, Pa — 1 autographed book "The Medical Treatment of Gall Bladder Disease",
- Dr Arthur Havley Sanford (Fellow), Rochester, Minn — 1 book, "Clinical Diagnosis by Laboratory Methods",
- Dr W D Sansum (Fellow) and Dr R A Hare (Fellow) Santa Barbara, Calif — 1 autographed book, "The Normal Diet and Healthful Living",
- Dr LeRoy Sante (Fellow) St Louis, Mo — 2 books (1) "Manual of Roentgenological Technique", (2) "Injuries to the Bones and Joints, Roentgenologically Considered",
- Dr Torald Sollmann (Fellow) Cleveland Ohio — 1 autographed book "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology",
- Dr J W Torbett (Fellow), Marlin, Tex — a book of poems, "Centennial Songs"

Reprints

- Dr Grafton Tyler Brown (Fellow), Washington, D C — 1 reprint,
- Dr Charles R Castlen (Fellow), Glendale, Calif — 1 reprint,
- Dr Charles Walter Clarke (Fellow), New York, N Y — 1 survey, "Control of Syphilis and Gonorrhea in the Scandinavian Countries and Great Britain",
- Dr A R Foss (Fellow), Missoula, Mont — 2 reprints,
- Dr D Waldo Holt (Fellow), Greensboro, N C — 1 reprint,
- Dr Herbert T Kelly (Fellow), Philadelphia, Pa — 2 reprints,
- Dr George R Minot (Fellow), Boston Mass — 1 reprint,
- Dr Kenneth Phillips (Fellow) Miami, Fla — 2 reprints,
- Dr Ellen C Potter (Fellow), Trenton, N J — 1 reprint,
- Dr William B Rawls (Fellow), New York, N Y — 1 reprint,
- Major James S Simmons (Fellow), (MC), U S A — 2 reprints
- Dr Walter M Simpson (Fellow), Dayton, Ohio — 3 reprints,
- Dr George E Wakerlin (Fellow), Louisville, Ky — 2 reprints,
- Dr W H Watterson (Fellow), La Grange, Ill — 2 reprints,
- Dr Marcos Fernan-Nunez (Associate), Milwaukee, Wis — 1 reprint,
- Dr Hyman I Goldstein (Associate), Camden, N J — 1 reprint,
- Dr Walter E Leonard (Associate), Hollywood, Calif — 2 reprints,
- Dr Charles B Sanders (Associate), Dallas, Tex — 3 reprints
- Dr Francis H Sleeper (Associate), Worcester, Mass — 2 reprints

The Legation of the Dominican Republic, Washington D C, has contributed to the Library a book, "President Trujillo—His Work and the Dominican Republic"

At the Annual Clinic Day conducted at the Memorial Hospital, Pawtucket, R I, on November 4, 1936, the guest speakers were as follows

- D₁ John Eiman (Fellow), Assistant Professor of Pathology, Graduate School of Medicine, University of Pennsylvania, "Observations on Hypo and Hyper Chloremia",
- D₁ George Morris Piersol (Fellow), Professor of Medicine, University of Pennsylvania, "Importance of Restoring and Maintaining Proper Chemical Balance in Chronic Renal Conditions",
- Dr H L Bockus (Fellow), Professor of Gastro-Enterology, Graduate School of Medicine, University of Pennsylvania, "Regional Ileitis and Ileocolitis",
- Dr H B Wilmer (Fellow), Assistant Professor of Medicine, Graduate School of Medicine, University of Pennsylvania "Glucose Tolerance and Metabolism in the Allergic Individual",
- Dr William D Stroud (Fellow), Professor of Cardiology Graduate School of Medicine, University of Pennsylvania, "Result of Five Years' Study at Pennsylvania Hospital of Various Digitalis Preparations and the Present Attitude Towards Digitalis in the Treatment of Cardio-Vascular Disease"

At last year's clinic the guest group was headed by D₁ James H Means (Fellow) of Boston, Mass The chairman at these meetings is Dr John F Kenney (Fellow) of Pawtucket, R I

Dr Thomas Parran, Jr, Surgeon General of the U S Public Health Service, addressed the College of Physicians of Philadelphia November 14 on "Social Diseases from the Public Health Point of View" The lecture was given under the auspices of the James M Anders Fund, established by the late Dr Anders (Master)

Dr Howard M Jamieson (Fellow), formerly of Wilkes-Barre, Pa, has been appointed Chief of the Pathological Department of the Loughborough and District General Hospital, at Loughborough Leicestershire, England

D₁ Porter Paisley Vinson (Fellow), formerly with the Mayo Clinic at Rochester, Minn, has accepted the appointment as Professor of Bronchoscopy Esophagoscopy and Gastroscopy in the Medical College of Virginia His new address is 300 Medical Arts Bldg, Richmond Va

Dr George Herimann (Fellow), Professor of Clinical Medicine in the University of Texas Medical School, conducted a clinic on "Faints and Fits or Syncopal Attacks" and presented a paper on "Some Newer Aspects of the Problems of Heart Failure" as the guest of the Section of Medicine of the Michigan State Medical Society, Detroit, on September 23, 1936

Dr James Alexander Miller (Fellow and Ex-President), Professor of Clinical Medicine, College of Physicians and Surgeons of Columbia University, has been elected President of the New York Academy of Medicine for a term of two years, Dr Arthur F Chace (Fellow) was elected Vice-President for three years

Dr George A Sherman (Fellow), is now Medical Director of the Oakland County Tuberculosis Sanatorium Pontiac, Mich

Dr Salvatore Lojacono (Fellow), formerly Superintendent of the Morgan Heights Sanatorium, Marquette, Mich, has joined the Staff of the Desert Sanatorium of southern Arizona, Tucson, October 1, 1936

Dr Max Pinner (Fellow), has now established his final and official headquarters at the Hermann M Biggs Memorial Hospital, Ithaca, N Y

Dr Charles R Castlen (Fellow) has resumed practice, after a period of illness, at 501 Glendale Professional Bldg, Glendale, Calif Dr Castlen was formerly located in Seattle, Wash

Dr Edward E Cornwall (Fellow) and Dr Frank Bethel Cross (Fellow) are respectively Chairman and Secretary of the new Section on History of Medicine of the Medical Society of the County of Kings (Brooklyn, N Y)

Dr Cross is also President of the recently reorganized Brooklyn Society of Internal Medicine

Dr Anthony Bassler (Fellow), New York, N Y, will be the guest speaker at the New Orleans Graduate Medical Assembly, March 8 to 12, 1937 The subjects he will present are "Hepatic Insufficiencies in Relation to Bodily Disorders" and round table talks on (a) "A Consideration of Diagnostic Criteria of Peptic Ulcer and Its Treatment", (b) "The Dysenteries—Amebic and Bacillary", (c) "Discussion on Biliary Tract Disease"

The Second Congress of the International Society of Gastroenterology will be held in Paris, France, September 13 to 15, 1937 The subjects to be discussed are "The Diagnosis of Gastric Carcinoma" and "The Acute and Chronic Occlusions of the Small Intestine" This Congress will be followed immediately by the International Congress on Hepatic Insufficiencies to be held in Vichy (ninety miles from Paris) on September 16 to 18 The United States National Committee of the International Society of Gastroenterology has been formed by representatives of the various gastroenterological societies in this country Dr Anthony Bassler (Fellow), New York, N Y, Dr Hyman I Goldstein (Associate), Camden, N J, Dr A C Ivy (Fellow) and Dr Lathan A Crandall, Jr, both of Chicago, and Dr Norman W Elton (Reading, Pa) compose the American group who will present the subject "The Relation of Hepatic Insufficiency to General Nutrition and Especially to the Nervous System" Information concerning membership may be obtained from the President, Dr Anthony Bassler, 121 East 71st Street, New York City

The program of the Eleventh Series of Friday Afternoon Lectures at the New York Academy of Medicine discloses a number of the Fellows of the College as contributors

November 6, 1936 "The Early Diagnosis and Treatment of Hypertensive Cardiovascular Disease," by Dr W W Herrick (Fellow), Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University,
 November 13, 1936 "The Gall Bladder Problem," by Dr Martin E Rehfuess (Fellow), Clinical Professor of Medicine, Jefferson Medical College,
 January 15, 1937 "Recent Advances in the Treatment of Chronic Arthritis," by Dr R Garfield Snyder (Fellow), Chief of the Arthritis Clinic, Hospital for the Ruptured and Crippled, New York City,

January 22, 1937 "Recent Advances in the Endocrine Field," by Dr David P Bair (Fellow), Professor of Medicine, Washington University,
February 26, 1937 "Modern Concepts of Anemia from the Clinical Standpoint," by Dr Edward B Krumblhaar (Fellow), Professor of Pathology, University of Pennsylvania School of Medicine,
April 2, 1937 "The Diagnosis and Management of the Commoner Clinical Allergies," by Dr Robert A Cooke (Fellow), Assistant Professor of Clinical Medicine, Cornell Medical College,
April 9, 1937 "A Study of Four Hundred Cases of Pulmonary Tuberculosis," by Dr George Foster Herben (Fellow), Physician in Chief, Loomis Sanatorium

Dr Guy W Carlson (Fellow), Appleton, Wis, is President of the Outagamie County (Wisconsin) Medical Society and Secretary of the Sixth Councilor District of the Wisconsin State Medical Society

Dr John H Peck (Fellow), Des Moines, Iowa, has removed to Oakdale, Iowa, where he has accepted the appointment as Superintendent of the Iowa State Sanatorium, November 1, 1936, to fill the unexpired term of Dr J A Edwards, who was killed in an automobile accident during October

Dr J C Kamp (Fellow), Casper, Wyo, has just completed an extended visit to the clinics and hospitals of London and Vienna

Dr Alexsei Leonidoff (Associate) addressed the Dutchess Putnam Dental Society October 29 on 'Diseases of the Heart and Lungs,' pointing out their relations to dentistry

Dr Alfred R Masten (Associate) has been appointed Director of the Division of Tuberculosis Control, Colorado State Board of Health, with offices at 424 State Office Bldg, Denver, Colo

Dr James B Collip (Fellow), Professor of Biochemistry, McGill University Faculty of Medicine, Montreal, Que, received the honorary degree of doctor of science during the Centenary of Harvard University in September

Dr William Thallmer (Fellow) is in charge of the Manhattan Convalescent Serum Laboratory, which has been established in the research laboratory of the department of health for preparation and distribution of immune serums for measles, scarlet fever and other communicable diseases

Dr J Burns Amberson, Jr (Fellow) and Dr Edgar Mayer (Fellow), New York City, have been appointed consultants on dust diseases by the State Industrial Commissioner

Dr Martin L Stevens (Fellow), Asheville, N C, has been appointed a member of the Board of Trustees of the State Tuberculosis Sanatoria

Dr Paul P McCain (Fellow), Superintendent of the State Sanatorium, Sanatorium, N C, was the recipient of the honorary degree of doctor of laws at the annual commencement of the University of North Carolina

Dr Henry A Christian (Fellow) delivered the third Frank Billings Lecture of the Thomas Lewis Gilmer Foundation of the Institute of Medicine of Chicago at a joint meeting with the Chicago Society of Internal Medicine, October 26, on "Edema, Diuretics, Diuresis"

Under the presidency of Dr Frank H Krusen (Associate), Rochester, Minn, The Academy of Physical Medicine held its annual meeting in Boston, October 20 to 22

Dr Jonathan C Meakins (Fellow), Montreal, Que, assisted in the presentation of a symposium on integration of the medical curriculum during the forty-seventh annual meeting of the Association of American Medical Colleges, Atlanta, Ga, October 26 to 27

Dr Chester W Waggoner (Fellow), Toledo, has been appointed a member of the Ohio State Medical Board

Dr Carl S Mundy (Fellow) and Dr Paul M Holmes (Fellow) have been appointed members of the Advisory Health Board, recently created for Toledo. The Board will act in an advisory capacity on all municipal health matters and will confer with the city manager, the health commissioner and the welfare director on current health problems

Under the Presidency of Dr Charles M Griffith (Fellow), Medical Director of the Veterans Administration, Washington, D C, the forty-fourth annual meeting of the Association of Military Surgeons of the United States was held at Detroit October 29 to 31. Dr Perceval S Rossiter (Fellow), Surgeon General of the U S Navy, was installed as President for the coming year. Among Fellows contributing to the program were

Dr Philip B Matz, Washington, D C, "Diabetes Mellitus among Veterans of the World War",

Dr Frederick G Buesser, Detroit, "Treatment of Peptic Ulcer",

Dr William W Hall, (MC), U S Navy, "Active Immunization against Tetanus with Tetanus Toxoid"

Dr John C Ruddock (Fellow), Los Angeles, President of the California Heart Association, gave an illustrated lecture before the seventh annual postgraduate symposium on heart disease of the San Francisco County Medical Society, November 18 to 19

Dr Ernest E Irons (Fellow), Chicago, gave a clinic on pneumonia and Dr Fred M Smith (Fellow), Iowa City, directed a symposium on peptic ulcer in connection with the annual clinic of the University of Iowa College of Medicine, held at Iowa City, November 12 to 14

Dr Edwin W Gehring (Fellow) has resigned as Editor-in-Chief of the *Maine Medical Journal*. The Journal will be continued under the direction of its Editorial Board

The University of North Carolina in connection with its extension division and its School of Medicine is sponsoring a graduate course of lectures in Goldsboro for physicians in the eastern section of the State. Dr Thomas Fitz-Hugh (Fellow), Philadelphia, and Dr Paul D White (Fellow), Boston, were those selected to give the lectures on "Common Forms of Anemia" and "Coronary Diseases," respectively

Dr J Morrison Hutcheson (Fellow), was installed as President of the Medical Society of Virginia during October

Dr David P Barr (Fellow), St Louis, will deliver the Nathan Lewis Hatfield Lecture before the College of Physicians of Philadelphia, January 6, on "Parathyroids and Their Role in Health and Disease". Dr Barr will deliver an address before the New York Academy of Medicine January 22 on "Recent Advances in the Endocrine Field". Dr Barr delivered a lecture on endocrinology at the Medical Institute of the University of Toledo, November 6, on the occasion of its third annual "Postgraduate Day"

Dr Ralph A Kinsella (Fellow), St Louis, addressed the Southwestern Medical Association at its twenty-third annual meeting at El Paso, November 19 to 21, on "Career of the Heart, Differential Diagnosis of Rheumatic Fever"

Dr Arthur C Christie (Fellow), Washington, D C, delivered the Silvanus Thompson Lecture before the British Institute of Radiology at Westminster, December 2

Dr Reginald Fitz (Fellow), Wade Professor of Medicine, Boston University School of Medicine, and Director of the Evans Memorial Hospital, has been appointed Lecturer on the History of Medicine, Harvard University Medical School, for three years. Dr Fitz is university marshal at Harvard and was formerly Associate Professor of Medicine in the Harvard Medical School before accepting the Wade Professorship at Boston University

Dr Horton R Casparis (Fellow), Professor of Pediatrics, Vanderbilt University School of Medicine, Nashville, was the guest speaker at the annual dinner of the Minnesota Public Health Association, Minneapolis, November 13

Dr Allen K Krause (Fellow), Baltimore, addressed the Brooklyn Thoracic Society, October 16, on "Modern Management of Clinical Tuberculosis"

Dr Paul P McCain (Fellow), Medical Director and Superintendent of the North Carolina Sanatorium for the Treatment of Tuberculosis has been appointed manager of a new state sanatorium now under construction at Black Mountain, near Asheville. A unit of the new hospital will be finished by April, 1937. Dr McCain will have charge of both institutions, with assistant managers at each

The Philadelphia County Medical Society adopted a new plan for meetings of its branch societies by arranging a symposium on the diagnosis of syphilis, the symposium being presented in turn before each branch. The speakers were

Dr Jefferson H. Clark (Fellow), laboratory aspects,
Dr Sigmund S. Greenbaum (Fellow), lesions of the skin and mucous membranes,
Dr William Egbert Robertson (Fellow), cardiovascular syphilis,
Dr Michael A. Burns (Fellow), syphilis of the nervous system

Dr James E. Paullin (Fellow), Atlanta, was elected President of the American Clinical and Climatological Association at its annual meeting in Richmond, Va., October 26 to 28.

On the program appeared Dr. Howard F. Root (Fellow), Boston, "Insulin Protamine in Treatment of Diabetes", Dr. Frederic M. Hanes (Fellow), Durham, N. C., "Metabolic Studies in Sprue", Dr. Edgar Mayer (Fellow), New York City, "The Dietary Treatment of Tuberculosis—More Recent Aspects", Dr. Lewis J. Moorman (Fellow), Oklahoma City, "Calcification of the Spleen", Dr. Roy R. Snowden (Fellow), Pittsburgh, "Treatment of the Thyroid Crisis"

Dr. Edward J. Murray (Fellow), Lexington, Ky., has been chosen President of the Southern Tuberculosis Conference

Dr. Roland N. Klemmer (Fellow), Lancaster, Pa., was recently elected as Chief of the Medical Department of the Lancaster General Hospital



DR H F STOLL

OBITUARIES

DR HENRY FARNUM STOLL

Henry Farnum Stoll, M D (Fellow and College Governor for Connecticut), Hartford, Connecticut, died September 28, 1936

Dr Stoll was born in Port Jervis, New York, May 25, 1878, the son of Albert and Elizabeth Farnum Stoll. He received his preliminary education in the public schools of Port Jervis, attended Cornell for two years and then took his medical training at Columbia University, College of Physicians and Surgeons, from which he graduated in 1902

Following his graduation, Dr Stoll served an internship at the Hartford Hospital and then began the practice of medicine in Hartford, Connecticut. His professional career was devoted to internal medicine, to the literature of which he contributed fifty-nine articles. His contributions on the subject of tuberculosis are outstanding, numbering twenty-five

In 1905 Dr Stoll became Assistant Physician to the Hartford Hospital, Assistant Visiting Physician in 1910 and Visiting Physician from 1923 until his death. He also held numerous hospital appointments throughout Connecticut as Consulting Physician

During the World War Dr Stoll served in the Medical Corps of the Army as Captain and Major, being assigned as Instructor in the Diagnosis of Tuberculosis, Army Medical School, Washington, D C

Dr Stoll became a Fellow of the American College of Physicians on April 8, 1929 and Governor for Connecticut in 1930. The College meant a great deal to Dr Stoll and its welfare interested him deeply. He was a member of numerous other medical societies, local, state and national, and a past president of the Hartford County Medical Society

On September 19, 1911, Dr Stoll married Miss Eleanor Roberts who, with his daughter, Miss Hortense Stoll, survives him

Dr Stoll was an energetic, arduous worker and student. His devotion to Medicine, his eagerness in the search for better methods of diagnosis and treatment, and his wise counsel long made him an outstanding medical consultant in Connecticut. Possessed too of a delightful sense of humor he was a most genial friend and companion

With the passing of Dr Stoll, another great physician has been taken from us. Of him one of his own patients has well said, "Though his presence will be keenly missed, the memory of his indomitable spirit will endure through the years and be a source of strength to those who were fortunate enough to be numbered among his friends"

OTTO G WIEDMAN, M D , F A C P

DR ROBERT SPEAR

Dr Robert Spear (Fellow), East Chicago, Ind, died August 23, 1936, aged 68 years. He was a native of Cobourg, Ont. He graduated from the Faculty of Medicine of Trinity University, Toronto, Ont, in 1897.

He served with the U S Army in the World War, was a former member of the East Chicago School Board, and had been a member of the Staff of St Catherine's Hospital in East Chicago since the opening of the institution in 1929. He had practiced in this vicinity since 1897.

Dr Spear was a member of the Lake County Medical Society, the Indiana State Medical Association, the American Medical Association, and had been a Fellow of the American College of Physicians since 1925.

DR GORDON LEE HASTINGS

Dr Gordon Lee Hastings (Fellow), Little Rock, Ark, died September 14, 1936, at the age of 39. For the last three years he had served as Assistant State Health Officer and Director of Rural Sanitation of the Arkansas State Board of Health. He was a native of Virginia and was a graduate of Randolph Macon. His professional degree was conferred by the Medical College of Virginia. After serving an internship at the Stuart Circle Hospital in Richmond, he took postgraduate work at the Rockefeller Training Station at Indianola, Mississippi. In 1929, he came to Arkansas where he made an enviable record in public health work. He obtained a M P H degree in 1935 from the Harvard School of Public Health.

Shortly before his untimely death, Dr Hastings had been elected to the Assistant Professorship in the Department of Public Health Instruction of the University of Michigan. He was at his parental home visiting prior to taking up his new duties when he was suddenly stricken with an acute cardiac failure. He was married and had one son.

Dr Hastings was elected a Fellow of the American College of Physicians in 1934. He was also a member of the Pulaski County Medical Society, the Arkansas State Medical Association, the Southern and the American Medical Associations.

Not of the aggressive type but on the contrary, modest and unassuming, Dr Hastings nevertheless was an outstanding physician in his chosen field. His loss will be mourned not only by his family but by his former confreres and a host of friends.

OLIVER C MELSON, M D, F A C P,
Governor for Arkansas

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FURTHER STUDIES ON INTOXICATION WITH VITAMIN D ^{*}†

By I E STECK, M D, H DEUTSCH, A B, C I REED, Ph D, and H C
STRUCK, Ph D, *Chicago, Illinois*

WITH the extensive application of massive doses of vitamin D as a therapeutic agent in various clinical conditions ^{1, 2, 3, 4 5, 6, 7} numerous criticisms have arisen which may be summarized as follows

- 1 Hypervitaminosis D may produce symptoms of hyperparathyroidism
- 2 The therapeutic use of vitamin D is rational only in conditions of known deficiency
- 3 Animals experimentally treated with vitamin D concentrates have shown extensive calcium deposits in various tissues, and other pathological changes have been found There is, thus, danger of permanent injury to human subjects

It is not the purpose of this paper to discuss the therapeutic value of concentrated vitamin D in any clinical condition Only by more extensive clinical investigation can its therapeutic value be established finally

That vitamin D in massive doses may be toxic to any individual, animal or human, has been recognized in all stages of this series of investigations which was begun early in 1929, and its administration to human subjects has been governed accordingly It is the purpose of this paper to present evidence bearing on these questions The first of these questions has been discussed very thoroughly by Shelling,⁸ who concluded that the preponderance of evidence is against the view that the activity of vitamin D is dependent upon the functional integrity of the parathyroids and in favor of the existence of an antagonism between the two The second criticism is purely speculative If this idea held true very few therapeutic procedures now in use could be justified

* Received for publication September 26, 1936

From the Departments of Medicine and of Physiology, College of Medicine, University of Illinois, Chicago

† This investigation at various stages has been supported in part by grants from Mead Johnson and Company, the Graduate School Research Fund, University of Illinois, the American Academy of Arts and Sciences, the Wisconsin Alumni Research Foundation, the Committee on Therapeutics of the American Medical Association, and the Phi Rho Sigma Medical Fraternity

In considering the nature of the action of massive doses of vitamin D it is assumed that the action is very different from the physiological effects of small doses. It is so different, in fact, that the concentrated material may be considered tentatively as a different substance. At the same time there is some legitimate doubt as to the justification for this attitude.

TABLE I
Observations on Dogs Receiving Vitamin D

No	1000 units/ K/day	Days	Kidney Mg Ca/ 100 gm Dry Tissue	Max. Blood Ca	Microscopic		Wt Loss Per Cent	Other Symptoms of Toxicity	
					Cell Degen	Ca Stain			
1	500	8	671	19 90	5	5	40	Severe	Died in coma
2	500	9	212	21 60	5	5	32	Severe	Died in coma
3	500	9	—	—	—	—	28	Severe	Died in coma
4	500	11	—	—	—	—	38	Severe	Died in coma
5	200	18	—	—	—	—	44	Severe	Died in coma
6	200	10	—	—	—	—	34	Severe	Died in coma
7	130	7	598	16 36	4	3	30	Severe	Died in coma
8	125	12	52	23 30	1	0	23	Mild	Died of distemper
9	100	30	110	16 30	0	0	7	Mild	Died of distemper
10	100	6	676	14 98	3	1	19	Severe	Died of distemper
11	100	20	—	—	—	—	23	Severe	Died in coma
12	100	13	—	—	—	—	17	Moderate	Found dead
13	60	7	340	23 36	?	0	24	Severe	Died of distemper
14	60	13	540	23 29	1	1	20	Severe	Died in coma
15	60	8	685	18 16	—	—	9	Severe	Found dead
16	60	7	800	19 56	4	2	+17	Mild	Found dead
17	60	12	865	24 50	—	—	0	Severe	Found dead
18	60	13	1221	31 06	5	5	37	Severe	Died in coma
19	60	20	—	—	—	—	42	Severe	Died in coma
20	60	10	—	—	—	—	30	Severe	Died in coma
21	50	17	3464	27 00	5+	5+	15	Severe	Died in coma
22	50	43	119	18 90	1	0	21	Moderate	Found dead
23	50	35	—	—	—	—	10	Moderate	Allowed to recover
24	50	12	—	—	—	—	28	Severe	Died in coma
25	50	24	—	—	—	—	19	Severe	Died in coma
26	48	35	47	21 50	0	0	6	Mild	Fair condition when killed
27	38	10	2200	16 02	5	5	18	Severe	Died in coma
28	37	47	115	23 16	?	0	48	Mild	Good condition when killed except emaciate
29	35	73	1148	19 30	5	5	60	Severe	Died in coma
30	35	33	693	15 60	5	5	—	Severe	Poor condition when killed
31	35	23	597	16 47	5	5	35	Severe	Poor condition when killed
32	35	8	407	22 74	1	?	17	Mild	Died of distemper
33	35	60	—	—	—	—	26	Mild	Fair condition when killed
34	35	54	—	—	—	—	40	Moderate	Found dead
35	35	30	—	—	—	—	29	Severe	Found dead
36	35	26	—	—	—	—	42	Severe	Found dead
37	25	33	1214	19 38	4	4	13	Moderate	Good condition when killed
38	25	62	131	15 80	1	1	15	Mild	Good condition when killed

TABLE I—*Continued*

No	1000 units/ K/day	Days	Kidney Mg Ca/ 100 gm Dry Tissue	Max Blood Ca	Microscopic		Wt Loss Per Cent	Other Symptoms of Toxicity	
					Cell Degen	Ca Stain			
39	25	70	—	—	—	—	18	?	Good condition when killed
40	25	79	—	—	—	—	8	Moderate	Found dead
41	25	50	—	—	—	—	22	Severe	Died in coma
42	25	56	—	—	—	—	5	Severe	Died in coma
43	25	16	—	—	—	—	20	Severe	Died of distemper
44	20	38	228	13 26	0	0	0	0	Good condition when killed
45	20	41	186	12 90	0	0	3	0	Good condition when killed
46	20	67	174	11 78	0	0	5	Mild	Good condition when killed
47	20	83	203	12 02	0	0	0	0	Good condition when killed
48	20	120	93	11 00	0	0	+7	0	Good condition when killed
49	20	60	—	—	—	—	0	Mild	Died of distemper
50	20	93	—	—	—	—	0	0	Good condition when killed
51	20	80	—	—	—	—	7	?	Allowed to recover
52	20	55	—	—	—	—	0	0	Good condition when killed
53	20	40	—	—	—	—	0	0	Good condition when killed
54	15	62	212	16 85	?	0	5	Slight	Died from distemper
55	15	136	147	11 83	0	0	0	Slight	Good condition when killed
56	15	70	86	12 15	0	0	0	0	Good condition when killed
57	15	153	262	10 80	0	0	+16	0	Good condition when killed
58	15	56	248	11 50	0	0	0	0	Good condition when killed
59	15	61	—	—	—	—	+12	0	Good condition when killed
60	15	61	—	—	—	—	0	0	Good condition when killed
61	15	67	—	—	—	—	0	0	Good condition when killed
62	15	90	—	—	—	—	+10	0	Good condition when killed
63	15	47	—	—	—	—	0	0	Good condition when killed
64	15	30	—	—	—	—	5	0	Good condition when killed

Early experience with impure preparations of vitamin D, particularly abroad, has led to a great deal of misunderstanding and fear of overdosage on the part of those who have had little acquaintance with the fundamental mechanisms involved. This point has been adequately discussed by Bills.⁹ Suffice it to say that most of this earlier work must be disregarded when considering the effects produced by the highly purified preparations now available.

EXPERIMENTS ON TOXICITY OF VITAMIN D FOR DOGS

The effects of massive doses of vitamin D must be judged on the basis of the dose per unit body weight and not on the absolute size of the dose. When considered in this light the order of increasing susceptibility appears to run as follows: rat, dog, human, rabbit, with little difference between the dog and human, while the rat is very much more resistant, and the rabbit much less so.

In the experiments on dogs, vitamin D was administered in the form of a solution of activated ergosterol in corn oil* (1,000,000 units per gm) or of calciferol† dissolved in corn oil. Most of the administration was done orally. A few animals received intravenous injections in which form the material is slightly more effective. The results of experiments on 64 adult healthy dogs are shown in table 1. The daily dose ranged from 15,000 to 500,000 units per kilogram of body weight as shown in the first column. An effort was made to adjust the dose to decreasing body weight so that the ratio between the dose and the weight of metabolising tissue remained fairly constant.

The figures in the second column represent the actual number of days of administration of the vitamin D and, therefore, the number of days the animals *survived the treatment*. Usually those that did not die were killed on the day following the last dose, others within two to three days. With amounts greater than 50,000 units daily the average survival period was 12 days, with amounts between 20,000 and 50,000, 39 days, and with 20,000 units or less, 68 days.

At death, tissues were taken for chemical analysis and for microscopic examination. In an earlier report¹⁰ on analyses of 13 different tissues in a series of dogs, it was shown that the kidney is the most vulnerable of any tissue to the calcifying action of vitamin D. In order to conserve space, only the figures for the calcium content of the kidney are included. In all other tissues the findings were very inconstant. Analyses of tissues of normal dogs have shown a calcium content in the kidneys ranging from 29 to 301 mg per 100 gm of dried tissue with a mean of 85 mg. The calcium content in the kidneys of 33 of the 64 dogs is shown in the third column of table 1.

With a daily dose above 50,000 units per kg the average content of calcium in the kidney was 564 mg per 100 gm of dried tissue, between 20,000 and 50,000, 921 mg, and with 20,000 units or less, 183 mg. The lower average in the first group may possibly be related to the shorter period of survival. The average in the third group is obviously lower because the dose was not great enough to cause as much deposition.

In the fourth column the figures represent the maximum concentration of

* Supplied mainly by Mead Johnson and Company, also by Abbott Laboratories, Parke Davis and Company, and Winthrop Chemical Company.

† Supplied by Mead Johnson and Company, Winthrop Chemical Company, and Glaxo Laboratories.

plasma calcium found at any time. The level was not constant in any group. Very high levels were seldom constantly maintained. In figure 1 is shown the distribution of the figures observed in dogs in relation to the daily dose of vitamin D. It is obvious that there is little correlation between the two factors. With daily doses greater than 20,000 units per kg every animal at some time showed very high concentrations, but the level fluctuated greatly in each animal. With lower doses the figures are within the normal range for heparinized plasma.

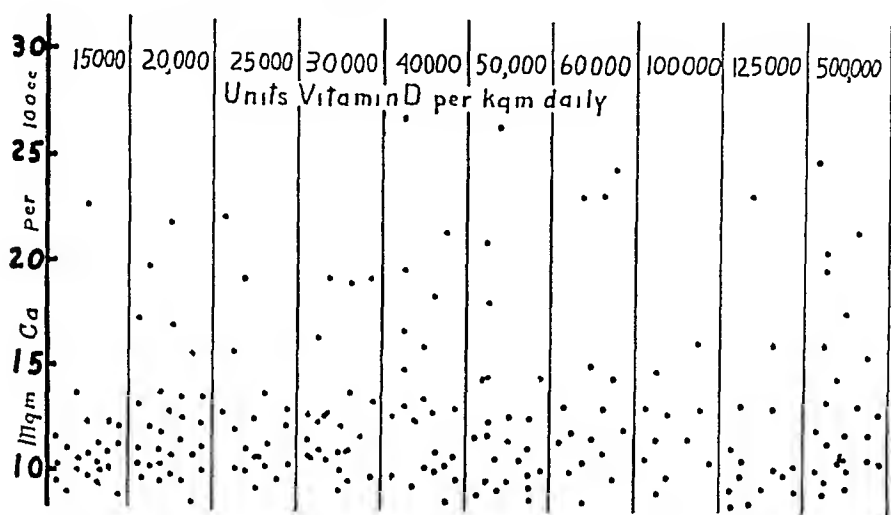


FIG 1 The blood calcium in 43 normal dogs under treatment with vitamin D. In each column are shown the total number of determinations made on all in each dosage group. Successive determinations on the same dog appear on the same ordinate.

For purposes of simplicity of recording and comparing the microscopic findings, a scale of 1 to 5 arbitrary units was used, although this method is open to some objection. The only striking microscopic findings were degeneration of individual cells and the presence of deeply stained areas of calcium deposition. In recording the degree of cell injury, a unit of 1 indicates the presence of only occasional degenerated cells, two or three in a single field. A unit of 5 indicates a stage in which considerable masses of contiguous cells had undergone degeneration. However, this stage always occurred in conjunction with a comparable stage of calcium deposition. It will be seen that the relationship between the degrees of cell destruction, calcium deposition and calcium content of the tissue varies considerably, but that in general those tissues having the higher calcium content by analysis showed the more extensive injury. These injuries appeared first and were most numerous in the collecting tubules but later were extended quite generally throughout the organ. In only one animal were calculi found in the tubules (No 21, table 1).

It appears that cellular injury occurs first and that calcium deposition then takes place at the sites of these injuries. In four animals (Nos 7, 18, 27, 31) showing extensive damage to the kidney, there was no evidence of

cellular injury nor of excessive calcium deposition in any other tissue examined

From evidence obtained on 12 other animals not included in the table, it appears that considerable loss of weight may occur before there is any evidence of injury to cells, but this was not invariably the case

Our observations do not confirm those of Appelrot¹¹ to the effect that hypervitaminosis D produces medial thickening in arteries. In only four of the 64 dogs examined, i.e., numbers 18, 21, 27 and 29, was this observed. In each case there was some medial thickening in the aorta and occasionally in smaller arteries

Loss of weight was marked in 36 out of the 43 dogs receiving more than 20,000 units per kg per day. One retained constant weight, one gained 17 per cent. As previously suggested,¹² the early weight loss appears to be due mainly to impoverishment of fat depots. When dog No 28 was examined at autopsy it was almost impossible to find any macroscopic fat deposits. This dog lost 48 per cent of the original weight, yet showed only mild objective symptoms of toxicity and was lively and active at the termination of the experiment. There was practically no microscopic evidence of cell injury. The plasma calcium was maintained at a higher average level over the period of the experiment than in any other animal in our experience.

On the other hand, dog No 21 lost only 15 per cent of the initial weight, although the kidney content of calcium was higher than in any other animal. These two animals serve to show clearly that weight loss is not an inevitable accompaniment of fatal intoxication in dogs.

One of the characteristic features of fatal hypervitaminosis D is the premortal coma. This condition is usually, though not always, preceded by partial paralysis, slow, shallow respiration, fine, thready, rapid pulse, salivation, and often by psychic changes of such a nature that a previously tame, friendly dog may become unmanageable and even vicious. Very often the symptoms resemble those following an injection of oil of wormwood. This condition may persist for several days but usually appears from two to three hours before death. It is probable that all of the dogs labelled "found dead" passed through this stage during the night, but the actual train of symptoms could not be observed. None of the animals that were killed were in this stage.

The objective symptoms of toxicity were much the same as those previously described for the human,⁴ such as weakness and lassitude, anorexia, polydipsia, polyuria, psychic disturbances, diarrhea. Bloody feces were passed by 11 of the 64 dogs. In addition, petechial hemorrhages were found in the mucosa of the stomach and intestines at autopsy.

With eight exceptions all of the 43 dogs receiving more than 20,000 units per kg per day died spontaneously. Nine of these died from distemper. Of the nine, three were in such a condition that early death in coma was predictable. Of the eight exceptions, one was allowed to recover. Of

the seven that were killed, two would probably have died. The other five would probably have recovered with cessation of the treatment.

Among the 20 dogs receiving 20,000 units or less per kg there were no evidences of cell injury, insignificant weight loss, very little evidence of toxic symptoms, and with the exception of two dogs that died from distemper and one that was allowed to recover all were in good condition when killed.

Thus, it may be concluded that vitamin D up to 20,000 units per kg per day for periods ranging up to 153 days is not seriously injurious to normal dogs. In greater amounts there is a wide range of susceptibility entirely unpredictable from any data at present available.

That the toxic effects may be characterized as true hypervitaminosis D is proved by the fact that in four instances (numbers 7, 17, 29, 34) the vitamin preparation administered was crystalline calciferol (40,000,000 units per gm) in solution in corn oil. This preparation contained *no* toxic by-products and yet the results were quite comparable with those from the same dose of activated ergosterol which may contain some inert material but practically no toxisterol.

In another series of experiments the dogs were brought to a stage of extreme toxicity with vitamin D and the administration was then discontinued. The state of toxicity was manifested by loss of weight, anorexia, listlessness and paralysis, and, in six animals, prostration. After varying intervals, when there was objective evidence of complete recovery, the animals were killed and subjected to the same examination as in the other series. The results are shown in table 2. In the first column are shown the periods

TABLE II

No	Days	Recovery Days	Units/K/Day	Kidney Ca	Max Blood Ca	Microscopy		Wt Loss Per Cent	
						Cell Degen	Ca Stain		
1	24	126	15,000	257	18.59	0	0	6	Good condition
2	15	9	20,000	48	19.89	0	0	13	Good condition
3	80	102	20,000	212	17.41	0	0	7	Good condition
4	10	48	25,000	323	22.13	0	0	30	Good condition
5	5	113	30,000	240	19.14	0	0	43	Good condition
6	5	107	35,000	242	19.43	0	0	30	Good condition
7	35	20	50,000	151	16.87	0	0	10	Good condition
8	18	115	50,000	272	14.62	0	0	29	Good condition
9	26	38	50,000	300	19.30	0	?	45	Fair condition
10	15	8	105,000	218	18.72	—	—	30	Still 15 per cent under weight Fair condition 10 per cent under weight

of administration of the vitamin, in the second the daily dose per kg, and in the third the recovery interval allowed. Actually in the dogs No 4, 6, 7 and 8 complete recovery of weight was accomplished in 53, 86, 73 and 60 days respectively. Animals No 9 and 10 were killed before weight

recovery was complete because both were definitely overweight when the experiments were begun

Eight additional dogs were originally included in this series but all of these were in the terminal stages of toxicity described above when the treatment was discontinued, and all died within two to seven days. Six of these were already prostrate when administration was discontinued.

In all but one (dog No. 4) the kidney content of calcium was within the normal range, although all showed figures in the higher limits of the normal range except Nos. 2 and 7. The average weight loss approximated that in comparable dosage ranges in the first series.

The maximum concentrations of plasma calcium observed were all high. Microscopic examination of the tissues showed no definite evidence of calcium deposition and no cellular injury. In Nos. 2 and 5 there was some distortion of the collecting tubules in the kidney by fibrosis. No vascular lesions were found.

From these experiments it appears that dogs may recover from extreme stages of toxicity and that whatever tissue injury occurs may be repairable. In extremes the result may be fatal before repair can be effected.

In the experiments on animals reported by others, so far as the potency of the dose can be calculated, toxicity has occurred only with doses above 20,000 units per kg. per day. Since the relation of dosage to weight has not been stressed before, many other workers have failed to record data which would make it possible to calculate the dose in terms of units per kilogram.

In both of our series it is apparent that the total amount of vitamin administered is not the most important determinant of the degree of toxicity since large doses have been tolerated well over long periods while smaller doses have produced drastic effects in a few days. Nor is the magnitude of the daily dose the sole factor. In general both dogs and human subjects appeared to be less sensitive during winter months.

TABLE III

Dog No	1	2
Units/kg./day	60,000	30,000
Initial plasma Ca	11.60	10.89
5th day	12.03	14.62
7th day	12.00	13.90
14th day	14.00	12.44
15th day	11.30	11.79
16th day	12.57	11.12
21st day	12.10	12.15
22nd day	11.34	—
23rd day	12.00	13.25
24th day	dead	—
26th day		12.24
30th day		9.70
31st day		13.00
32nd day		11.93
33rd day		dead

It has been emphasized many times that the diet is a very important factor in conditioning toxicity. All of these animals were kept on the stock kennel diet throughout and no variations were introduced at any time.

It is also apparent that the concentration of plasma calcium is not closely correlated with toxicity. Many investigators have been inclined to use the terms "hypercalcemia" and "toxicity" interchangeably. Many experiments have been done which clearly disprove a causal relation between these conditions but the two experiments reported in table 3 will serve to illustrate the point. Both of the animals showed some hypercalcemia, but it was by no means pronounced. Number 1 received twice the dose of number 2, but except for the earlier death there was no striking difference. When one contrasts these figures with the high figures for some of the animals that survived as in tables 1 and 2, it is a fair assumption that hypercalcemia per se is not the cause of toxicity.

OBSERVATIONS ON HUMAN SUBJECTS

The enormous absolute doses of vitamin D that have been administered to human subjects have naturally aroused some question. If, however, one bears in mind that human and canine susceptibility seem closely approximated, and if one gives due consideration to the weight/dosage relationship, it appears that few of the human subjects have ever received amounts comparable to the highest doses tolerated by the dogs of this series.

TABLE IV

	Male			Female		
	Total No	No Toxic	Per Cent	Total No	No Toxic	Per Cent
Postoperative tetany	2	0	0	15	4	26.4
Hay fever and asthma	178	13	7.3	322	24	7.4
Arthritis	43	5	11.6	107	11	9.4
Miscellaneous	12	1	8.3	23	3	13
Normal subjects	63	1	1.5	8	1	12.5
	298	20	6.7	475	43	9
Total subjects					773	
Number toxic					63	
Per cent toxic					8	

Table 4 shows the status of 773 human subjects who have received amounts of vitamin D above 100,000 units daily. The doses routinely given ranged upward from 200,000 units total daily dose for periods ranging from seven days to five years. With such a dose a 50 kilo subject would receive only 4,000 units per kg per day. With 300,000 units a 60 kg subject would receive 5,000 units per kg per day. This table, of course, does not take into account the varying dosages, so that one cannot draw conclusions as to comparative susceptibility in the various groups of subjects. However, it ap-

pears, from other statistics too voluminous to include here, that the order of decreasing susceptibility among the different groups of patients is arthritis, normal subjects, hay fever alone, hay fever with asthma, tetany

TABLE V

Units/kg /day	No	No Toxic at any Stage	Per Cent Toxic
1500-3000	5	5	100
3000-5000	555	25	4.5
6000-7000	123	18	14.6
8000-15,000	70	11	15.7
15,000-25,000	16	3	18.8
25,000-35,000	4	1	25
	773	63	8+

In table 5 the incidence of toxicity at each range of dosage is shown. This analysis does not take into account the duration of administration since, as was indicated by the experiments on dogs, the total amount does not seem to be the most important factor. Nor does it take into account the effect of simultaneous administration of yeast as a protective measure which was done with many human subjects. This procedure has already been discussed rather fully.^{4, 5} The first five subjects may be disregarded since they became nauseated from corn oil as readily as from viosterol, so that they do not represent true hypervitaminosis D, but rather some kind of sensitivity not related to the vitamin. It is probable that some of those subjects included in the toxic groups at higher dosage were of this type. The shortest period of administration that produced intoxication in the group on 3,000 to 5,000 units per kg per day, was 87 days. Since the condition in this instance developed very suddenly and without any weight loss, it is possible that some unrecognized disturbance rendered the subject temporarily more susceptible. On discontinuance of administration of vitamin D prompt recovery occurred, and four days later the treatment was resumed and continued four months without further disturbance.

In the group on 6,000 to 7,000 units per kg per day the shortest period for development of toxicity was 60 days. In this instance there was a loss of four pounds in two days. The condition was abated sufficiently to resume only after eight days without treatment. A second mild intoxication occurred three months later.

In the last two groups the high doses were not continued beyond 10 days except in one case, regardless of whether intoxication occurred. In this case one of the authors, a normal subject, took 35,000 units per kg per day (3,000,000 units total daily) for 15 days without any evidence of disturbance of any kind.

Vrtaak and Lang⁷ have recently reported 100 per cent incidence of toxicity in a series of 22 human subjects to whom massive doses of vitamin D

were administered. The discrepancy between this high incidence and the relatively low incidence in our series is difficult to explain at present.

The symptoms of hypervitaminosis D in human subjects were described fully in an earlier paper.⁴ It remains now to correlate these findings with the experimental results on animals. Tentatively we suggest that the course of events is as follows. First, cellular degeneration occurs, more commonly in the kidney. Concurrently there may be loss of weight and other objective symptoms. If weight loss occurs before other symptoms it is probably due solely or mainly to increased fat catabolism. Second, deposition of calcium occurs at the sites of cell injury, apparently this does not occur except as a secondary result of such injury. Third, up to advanced stages of toxicity these processes may be repairable in dogs if the vitamin D administration is discontinued.

From the results of previously reported work^{10, 12} it appears that the calcium removed from the tissues during recovery is excreted in the urine. At least, repair is not complete until the urine calcium excretion becomes normal.

The increased excretion of calcium that usually takes place^{12, 13} under massive administration of vitamin D in both human subjects and dogs is not, however, due solely to removal of the microscopic deposits in the soft tissues, because the increase in the urine begins before there is any microscopic or chemical evidence of excessive deposition in soft tissues. The source of this initial increase in the urine has not yet been determined, but from Shelling's discussion it probably comes from the trabeculae of the bones. Generally the average level of blood calcium is decreased after the excretion is increased.

We have made no examination of blood pressure in dogs, but a large number of the human subjects were examined at frequent intervals over long periods. Since there have been no significant changes the data are omitted. In most instances there seems to be some tendency to a slight decrease in the general level. This, of course, does not eliminate the possibility of medial proliferation in the arterioles.

Our human subjects ranged in age from 17 to 76 years. Older subjects were generally less readily intoxicated but recovered less readily when intoxication did occur, and seemed to be somewhat more sensitive thereafter.

There are on record only two instances of death in human subjects, certainly due to hypervitaminosis D, since the more highly purified preparations became available. One of these, recently reported by Thatcher,¹⁴ was probably a case of idiosyncrasy to vitamin D. It is difficult to determine from the report the unit dosage. However, it is clear that the administration was continued after intoxication was markedly developed.

We wish to stress that administration of vitamin D should be discontinued at once when the symptoms of intoxication appear. Neither animal nor human subjects in our experience have ever recovered from the toxic condition while administration continued.

The other case has not yet been reported in detail in the literature, but the reports of the coroner and the attending physician¹⁶ reveal the following facts. A physician, aged 74, weight 290 pounds, undertook self medication with a concentrated solution of activated ergosterol. Owing to an *error* in calculation of the dosage he received 2,300,000 units daily for 18 days or approximately 18,000 units per kg per day, a dose 10 times that intended. Since he was very obese the dose per kilogram of actively metabolizing tissue was much greater. The symptoms described were quite typical of hypervitaminosis D, with hypercalcemia, so that there is no doubt that in this case the treatment was the immediate cause of death. However, the presence of generalized arteriosclerosis suggests that this was a fundamental handicap to his recovery after discontinuing the treatment.

The administration of similar or larger amounts in our series without serious disturbance should not be interpreted to mean that such treatment can be undertaken without caution. In fact, our experience indicates clearly that administration of massive doses of vitamin D should not be undertaken for any cause except under the careful supervision of a physician who can and will carefully check the patient's condition at frequent intervals and who will see to it that the treatment is discontinued promptly on the appearance of the first signs suggestive of toxicity.

It is probable that any suggestion of kidney dysfunction should constitute an absolute contraindication. Until further information is available arteriosclerosis also should probably be considered a contraindication. Consequently, this form of treatment should be administered to older subjects only with extreme caution.

Nevertheless, if these precautions are observed, massive doses of vitamin D may be utilized therapeutically as safely as many other agents administered daily. That its misuse has resulted in death should not prejudice its controlled use under circumstances of possible value.

In view of the extensive experience in administration of vitamin D to human subjects with a relatively low incidence of toxicity, and the correlation of the results of animal experiments with the observations on human subjects, we believe that the burden of proof now rests on those who maintain the undesirability of the use of this form of therapy. Its actual practical value in particular clinical conditions will, of course, be determined only by more extensive clinical experience.

It must be admitted that the mechanism of toxicity is still unexplained. Our findings do not agree entirely with those of Ham and Lewis¹⁸. It is possible that the dose of approximately 600,000 per kg per day or more, which these observers administered to rats, was a factor in producing a different type of lesion. Up to the present time conceptions of the physiology of vitamin D have perhaps been too circumscribed because of its striking effect on calcium metabolism. That the thyroid plays an important part in the action of vitamin D is indicated by the results of another investigation¹⁷.

Also, it appears that the pathologic effects are greatly accentuated in a hypothyroid state. This *may* be an important factor in the variability in sensitivity to intoxication.

The results obtained by Gelfan¹⁸ on isolated frog muscle suggest that vitamin D exercises a catalytic effect in peripheral tissues. If this should be confirmed, it might serve as a forward step in explaining the injury to isolated cells in peripheral tissues. It is conceivable that the metabolism of individual cells might be accentuated to such a point as to result in the disintegration of the cells themselves. We have not been able to recognize the cellular changes preliminary to disintegration so that we can offer no explanation of the actual nature of this process.

SUMMARY AND CONCLUSIONS

1 Observations on 64 dogs and 773 human subjects receiving massive doses of vitamin D have been made and data recorded as to dose per unit of body weight, and on the nature of the process of intoxication.

2 Both human subjects and dogs generally survive the administration of 20,000 units per kilogram per day for indefinite periods without intoxication.

3 Hypervitaminosis D first produces cell injury followed by calcium deposition. This process is reversible and reparable if administration is discontinued promptly.

4 Intoxication for short periods does not result in any permanent injury that can be recognized by the methods employed in this investigation.

ADDENDUM After this manuscript was written there came to our attention a very comprehensive study by Cowdry and Scott¹⁹ on normal monkeys under treatment with vitamin D in which it was suggested that pathological changes may occur in tissues without clinical symptoms. However it was also suggested that there might be a species peculiarity.

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THE DIETETIC TREATMENT OF CONSTIPATION WITH SPECIAL REFERENCE TO FOOD FIBER

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THE non-cathartic treatment of constipation includes, among other recognized measures, treatment by diet (vegetables, cereals, fruits, fats and water), and treatment by artificial bulk producers (mineral oil, agar, bassorin, psyllium seed, cellulose and bran). In recent years the artificial products have dominated the literature and have perhaps unduly impressed the mind of the practitioner. Useful as they may be to meet temporary conditions, it is now becoming realized that these substances cannot be employed indefinitely without the possibility of some interference with nutrition (Bastedo,² Morgan¹²).

It therefore seems timely to refocus attention on the diet—for this after all must always remain the mainstay in treatment. Perhaps the most striking finding in examining the scientific basis for our clinical procedures in this connection is the fact that apparently no important quantitative studies on humans have made much impression on the clinical literature between the time of Rubner¹⁴ in the eighteen-eighties to the recent publications of such physiologists as Rose,¹³ Cowgill^{8,9} and their associates. Working with human subjects, as well as with experimental animals, these observers confirmed the fundamental axiom that there exists a quantitative relation between the amount of crude fiber ingested and the laxative result. Cowgill especially has clearly stated the criteria of laxation, has laid down the general procedure for the study of laxative substances on a fiber-equivalent basis, and has suggested that for normal men the physiologic fiber minimum for adequate laxation corresponds to a daily intake of 90 to 100 milligrams of fiber per kilogram of body weight. This worker confined his attention to the use of wheat bran as a laxative. In five constipated subjects two were relieved by a diet rich in fruits and vegetables, but three others required the addition of bran for comfort. It might be added that in none of the recent work is there any attempt to standardize the intake of fibrous foodstuffs in general, nor to compare the relative value of one of these articles with another.

In view of our thesis that constipation should be treated as thoroughly as possible by diet before calling upon artificial products for assistance, it would appear desirable for the physician to have a sound basis of precise information. In this regard, however, the current American books on diet are not very helpful. For even an approximate statement of the quantitative employment of diet in the treatment of constipation one must go back to von Noorden¹⁵. This author advocated the use of a bulky diet containing

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a daily intake of 300 to 500 gm (10 to 17 slices) of whole wheat bread, 80 to 100 gm of dried legumes (peas, beans, lentils) in the form of thick soup, and 10 to 15 large prunes (about 100 to 150 gm according to our standards) This diet gave von Noorden excellent results in Germany for over 25 years However, it is not equally practical for use in this country because of the persistent trend away from breadstuffs and legumes

For this reason, and because of their recognized superior laxative properties, fruits were selected as the subject of our study Prunes, apples and bananas were chosen because of their general attractiveness and availability and also for the following specific reasons Prunes, because of their ancient repute as cathartics and the recent discovery (Emerson¹⁰) that they contain an active principle similar to di-hydroxy-phenyl isatin, related to the commercial "isacen", apples, because of their wide popularity as "bowel regulators", and bananas, because of the possibility that their smooth texture might make them particularly useful in spastic or irritated colons

This experiment therefore was planned to determine the relative usefulness of these three fruits on a fiber-equivalent basis The prunes, apples and bananas used in our study possessed a fiber content of 1.9 per cent, 1.4 per cent and 0.6 per cent respectively, representing a ratio of 3 : 2 : 1 *

METHODS

The subjects selected for this study were nine hospital dietitians They were in good general health and carried on their regular work throughout the course of the experiment On the basis of their bowel function the subjects were classed as follows Regular, three subjects (5, 7, 8), irritable, two subjects (1, 3), constipated, four subjects (2, 4, 6, 9)

All four constipated subjects showed low basal metabolic rates (exceeding minus 10), on at least one occasion This finding, it must be confessed, surprised us and suggests an intimate relation between an individual bowel function and the thyroid secretion It also lends emphasis to what T R Brown⁴ has long maintained, namely, that constipation may in many instances be due to a "forme fruste" of myxedema

The experiment was divided into eight periods of at least nine days each as follows

Period I Preliminary Diet uncontrolled

Period II Low Fiber Basal Fiber content 33 mg per kg from miscellaneous sources

Period III First Banana Fiber content 33 mg per kg all from bananas

Period IV Prune "Low Fiber Basal" plus 33 mg fiber per kg from prunes, making a total of 66 mg fiber per kg

Period V Second Banana "Low Fiber Basal" plus 33 mg fiber per kg from bananas, making a total of 66 mg fiber per kg

* The figures for prunes and apples were obtained from actual laboratory analysis of fruit used in the experiment The fiber content of bananas was obtained from Circular No 50, U S Dept of Agriculture⁶

Period VI Apple "Low Fiber Basal" plus 33 mg fiber per kg from apples, making a total of 66 mg fiber per kg

Period VII Medium Fiber Basal Fiber content 66 mg per kg from miscellaneous sources (see table 1)

TABLE I
Diet Used in Period VII ("Medium Fiber Basal")
Weight of subject 57.2 kg
Total calories 2255
Fiber content 66 mg per kg

Distribution by Meals (Grams)		Food (Grams)				
			CHO	Pro	Fat	Fiber
<i>Breakfast</i>						
Grapefruit	125	Egg (1)	50	6.7	5.3	
Milk	200	Meat	100	20.6	11.6	
Shredded wheat	25	Milk	200	10.0	6.6	
Sugar	25	Bread	90	47.9	8.0	45
		Shredded wheat biscuit	25	20.5	2.6	53
		Potato	200	38.2	4.0	80
<i>Dinner</i>		Beets	100	9.6	1.6	90
Meat	100	Lettuce	75	2.2	9	45
Potato	100	Grapefruit	125	12.6	6	38
Lettuce	75	Cocoa		22.0	8.0	27
Mayonnaise	10	(milk 100				
Bread	30	(sugar 10				
Butter	15	(cocoa 6				
Cream	30	Custard				
Jelly	20	(egg $\frac{1}{2}$)		3.4	2.6	
Ice cream	60	(milk 100	5.0	3.3	4.0	
		(sugar 10	10.0			
<i>Supper</i>		Ice cream	60	14.7	6.4	
Egg (1)	50	Cream	60	1.8	24.0	
Potato	100	Jelly	40	30.9	4	
Beets	100	Butter	40		34.0	
Cocoa	200	Sugar	25	25.0		
Bread	60					
Butter	15					
Jelly	20					
Cream	30		250.4	71.0	108.1	3.78
Custard	135					

Period VIII Third Banana "Medium Fiber Basal" plus 33 mg fiber per kg from bananas, making a total of 99 mg fiber per kg (see table 2)

Except for Period I, which served as a control, the diets were weighed and so arranged as to fulfill the basic requirements as to caloric value, relative proportions of carbohydrate, protein and fat, and total fluid intake for the ideal weight for each subject. The fiber content was controlled throughout except in the first period, being modified from time to time according to the needs of the experiment. It also was calculated for the ideal weight for each subject. Whenever changes in fiber content were made, the caloric and basic factors were maintained by manipulating the fiber-free foods (e.g. butter, meat, milk, fruit juices) in the diet (see tables 1 and 2).

TABLE II

Diet Used in Period VIII ("Third Banana")

Weight of subject 57.2 kg

Total calories 2284

Fiber content 99 mg per kg

Distribution by Meals (Grams)		Food (Grams)				
			CHO	Pro	Fat	Fiber
<i>Breakfast</i>						
Banana	115	Egg (1)	50	6.7	5.3	
Milk	200	Meat	100	20.6	11.6	
Shredded wheat	25	Milk	200	10.0	6.6	
Sugar	25	Cocoa		22.0	8.0	27
		(milk 200)				
		(sugar 10)				
		(cocoa 6)				
<i>Dinner</i>						
Meat	100	Bread	90	47.9	8.0	45
Potato	100	Shredded wheat	25	20.5	2.6	53
Lettuce	75	Potato	200	38.2	4.0	80
Mayonnaise	10	Beets	100	9.6	1.6	90
Bread	30	Lettuce	75	2.2	.9	45
Butter	15	Grapefruit	125	12.6	.6	38
Cream	30	Cream	60	1.8	1.3	
Jelly	20	Jelly	40	30.9	4	
Grapefruit	125	Butter	40		34.0	
Banana	100	Sugar	25	25.0		
		Banana	315	66.4	4.1	1.89
<i>Supper</i>						
Egg (1)	50					
Potato	100		287.1	65.4	97.0	5.67
Beets	100					
Cocoa	200					
Bread	60					
Butter	15					
Jelly	20					
Cream	30					
Banana	100					

The periods were marked off from each other by the ingestion of a capsule containing approximately $7\frac{1}{2}$ grains of caimine or, if menstruation had to be considered, the same bulk of charcoal. A short basal period of three days was interpolated between successive experimental periods to allow for hangover effects. In addition the first two days of each period were disregarded for calculating laxation rates in order to discount any possible latent interval. In other words only the last seven days of each experimental period were used for the final statistics despite the fact that at least 12 days elapsed from the end of one experimental period to the end of another.

The laxation (number of stools) was recorded for each day of every period by each subject, the participants also noting the ease of bowel evacuation (subjective impression) and the character of the stools. In this paper the laxation is expressed in terms of stools per week per person.

The total colon emptying time was observed roentgenographically in five of the subjects during the first six periods of the experiment. This was accomplished by following the progress of a standard barium meal through the colon and rectum until all traces of barium were spontaneously eliminated. The opaque meal was not administered until the third or fourth day of each experimental period by which time the carmine or charcoal had been identified in the feces.

The normal total colon emptying time was determined from a review of 844 private patients previously published by one of us¹¹. It was found to be 72 hours. In the preliminary (control) period only one subject showed an emptying time of 72 hours. Of the rest, three emptied in 96 hours and one in 120 hours. These figures therefore furnished the base line for the present experiment, each subject being compared throughout with her original figures.

The weight of the stools was determined in the last two periods by actual measurement immediately after passage. This served as an additional check on laxation since it was found that the increased number of stools did not always mean that a laxative effect was being produced.

EXPERIMENTAL RESULTS

Period I (Preliminary) The diet was not controlled, each subject eating what she pleased but recording the following data: ideal weight (for height, age, sex), fiber intake per day, individual laxation rate.

The daily fiber intake was estimated from the individual records and was found to vary from 44 to 97 mg per kg. The average was 68 mg., or two-thirds of Cowgill's physiologic minimum. The group laxation (seven day total for nine subjects) was 73. The laxation averaged 8.1 stools per individual per week. This period was considered typical ("normal") by all but one participant, despite the fact that the extremes of laxation varied from a maximum of 13 to a minimum of three. The total colon emptying time averaged 96 hours, with one subject taking 72 hours (ideal), one, 120 hours, and the remaining three, 96 hours for evacuation of the standard opaque meal.

There was no absolute correlation between the fiber intake, laxation, and colon emptying time. The best showing was made in the roentgen-ray group by subject 1 with a fiber average of 71 mg per kg, laxation of 9, and colon emptying time of 72 hours. Subject 6 (not roentgen-rayed) took about the same amount of fiber, 75 mg, but had a laxation of 3. Subject 2 who felt more constipated than usual in this period had a fiber intake of 44 mg, a laxation of 10, but a colon emptying time of 120 hours. Two subjects (7 and 9) took about the same amount of fiber, 90 and 97 mg, respectively, but subject 7 had a laxation of 12 and subject 9 a laxation of 6 in this period. The four constipated individuals took 44, 55, 75, and 97 mg of fiber respectively. The highest intake was associated with a laxation of 6

Period II (Low Fiber Basal) The object of this period was to determine whether constipation could be produced at will by diminishing the fiber content of the diet to one-third the physiologic fiber minimum. Maintaining the energy and other basic requirements, the diet was prepared to supply a fiber content of 33 mg per kg of ideal weight—a fiber level which, according to Cowgill, should produce constipation. Such a result was indeed secured, the group laxation dropping to 58, the individual laxation to 64, and the colon emptying time increasing to 130 hours.

Every subject felt "constipated," the maximum individual laxation being 8, the minimum 1. The colon emptying time of subject 1 remained at 72 hours with 8 stools, but that of subject 2, also associated with a laxation of 8, was 168 hours. The colon emptying time of subject 6 (1 stool per week) was not studied because she was not in the roentgen-ray group, but was estimated as at least 240 hours.

Period III (Fruit Banana) This period was introduced to determine whether bananas contained any hitherto unknown laxative quality other than their fiber (and other carbohydrate) content. In order to test this possibility, the 33 mg of fiber (from miscellaneous sources) of the basal period were completely replaced by the same amount of banana fiber. In other words, all the fiber in this period was derived from banana exclusively. It took approximately three bananas (315 to 325 gm) to supply this amount of fiber. The group laxation was 60, the individual 66, the colon emptying time 81. In short, all the findings remained the same as in the basal period except for acceleration of the colon emptying time. It should be noted in this connection that five of the nine subjects menstruated during this period. Since laxation is usually increased by this function, the acceleration of the colon emptying time should probably be considerably discounted.

In view of the above findings, it was concluded that there is no evidence that bananas possess any special cathartic value in addition to that of their fiber (and other carbohydrate) content.

The diets for the next three periods were constructed according to a uniform plan. The basal diet contained 33 mg per kg of fiber derived from miscellaneous sources. To this were added 33 mg per kg of additional fiber, derived respectively from prunes, bananas and apples, according to the fruit studied in each period. The total fiber content of the diet was 66 mg per kg. It was decided not to exceed this level because reasonably satisfactory laxation had been produced in this group by a similar amount of fiber derived from miscellaneous sources (see Period I). Besides, it was thought that the ingestion of more than 33 mg per kg of fiber from a single fruit source would so overbalance the diet as to make it impractical for everyday use. Thus, for example, 66 mg of fiber per kg would mean 6 bananas per day, or 40 prunes, or 2½ apples.

Period IV (Prune) Approximately 20 small California prunes (100 gm edible portion) a day were required to yield 33 mg per kg of fiber.

The group laxation was 70, the individual laxation averaged 77 stools per week per person, the colon emptying time averaged 91 hours. Five subjects found prunes the most laxative of the three fruits tested. Two found them second best and two rated them least effective.

Period V (Second Banana) The same amount of banana was used as in the first banana period, but this was in addition to the 33 mg from miscellaneous sources of fiber. The group laxation was 62, the individual laxation averaged 68 stools per week per person, and the colon emptying time averaged 98 hours. One subject found bananas the most laxative fruit, three subjects gave it second place, and five subjects found it least effective.

Period VI (Apple) A daily average of $1\frac{1}{4}$ to $1\frac{1}{2}$ cored and peeled "Delicious" apples weighing 140 gm and served raw was required to yield 33 mg of fiber. The group laxation was 55, individual laxation averaged 61 stools per week per person, and colon emptying time averaged 115 hours. Three subjects found this the most laxative period, two found it the most constipating. The remaining four found it occupying an intermediate position, more laxative than bananas, less than prunes.

The next two periods were designed to determine the effect of a diet containing the physiologic fiber minimum (99 mg) in which one-third of the fiber was derived from fruit and two-thirds from miscellaneous sources. The first of these periods (Period VII) served as a control and contained 66 mg of fiber from mixed sources. Banana was the source of the fruit fiber used in the last phase of the experiment (Period VIII).

Laxation was determined not only by recording the daily number of stools per subject as heretofore, but in addition by weighing the fresh stools immediately after passage. The colon emptying time was not determined roentgenologically. Each period was of nine days' duration. As heretofore the periods were marked off by carmine or charcoal and only the last seven days in each case were used in the final calculations. Five of the nine subjects who volunteered for the first six periods were used in this study.

Period VII (Medium Fiber Basal) (see table 1) The diet contained 66 mg of fiber per kg for each subject, derived from miscellaneous sources. This period served as control to the final period.

Laxation was fairly normal for the period, averaging 35 stools for the group of five, or 7 stools per person per week. The weight of the stools averaged 670.6 gm per person per week.

Period VIII (Third Banana) (see table 2) The diet was the same as in Period VII, plus 33 mg of fiber derived from an average of three bananas daily, making a total fiber content of 99 mg per kg for each subject. As heretofore throughout the experiment this change was effected without altering the caloric or other values of the diet.

Laxation was increased to a group level of 38 stools, an average of 7.6

stools per person per week. The weight of the stools increased to 771.2 gm per person per week. Of five subjects tested, three showed a definite increase in laxation, and one showed practically no change. The fifth subject was apparently constipated by the banana diet. Among those whose laxation was increased was subject 6, the most constipated individual in the group. Her laxation rose from 3 in Period VII to 5 in Period VIII, and the stool weight from 385 to 740. Period VIII was rated by her equal to the apple period which had heretofore given the best laxation.

From the above experience it was concluded that the addition of approximately three bananas a day to an "average" diet (66 mg of fiber from miscellaneous sources) is moderately laxative. The effect can be expressed as an increase in the number of stools by 0.6 per subject per week, and an increase in the weight of the stools by 100 gm per subject per week.

EXPERIMENTAL CONCLUSIONS (see table 3)

According to the average laxation and colon emptying time, the laxative power of the three fruits when tested on a strictly fiber-equivalent basis (66 mg per kg) may be rated as follows. First, prunes with laxation of 7.7 and colon emptying time of 91 hours, second, bananas, with laxation of 6.8 and colon emptying time of 98 hours, third, apples, with laxation of 6.1 and colon emptying time of 115 hours.

TABLE III
Laxative Effect of Prunes, Apples, Bananas

Experimental Period	Total Stools per Week	Laxation per Person per Week	Colon Emptying Time Hours	Stool Weight Grams
I Preliminary	73	8.1	96	—
II First Basal	58	6.4	130	—
III First Banana	60	6.6	81	—
IV Prune	70	7.7	91	—
V Second Banana	62	6.8	98	—
VI Apple	55	6.1	115	—
VII Second Basal	35*	7.0	—	670.6
VIII Third Banana	38*	7.6	—	771.2

* Five subjects

On the other hand, the number of stools was not always an accurate guide to the laxative effect because some subjects felt that as they became more constipated they required more efforts to eliminate the same or smaller bulk of stool than they would if the feces were softer. It is for this reason, for example, that subject 9 rated apples (six stools per week) above bananas (eight stools per week).

Accordingly, if subjective criteria only are considered, the fruits rank as follows. Prunes gave the best laxation in five subjects, apples in three,

bananas in one, and conversely, bananas gave the poorest laxation in five subjects, apples in two and prunes in one

However, bananas cannot be considered constipating since in most cases they increased laxation when added to an "average" diet (total fiber 99 mg per kg). Similar results are reported by Bergeim³ who found that two bananas taken before lunch and dinner and at bedtime produced daily large soft stools in three constipated subjects. In fact, owing to their smooth texture and relatively low fiber content, bananas may prove of special value in constipation associated with an irritable colon (see below)

The effect on the individuals according to their classification in terms of original bowel function may be described as follows. The two subjects with irritable colon (1 and 3) tolerated the experiment without developing diarrhea at any of the fruit periods. One of these sensitive subjects preferred the effect of bananas to that of both the other fruits tested. The three subjects classed as "regular" all preferred the effect of prunes. Of the four constipated subjects three preferred apples and one prunes. The most constipated individual (6) rated apples first, bananas second and prunes last on the basis of subjective impression.

It is probable that the simultaneous employment of several sources of fiber is superior to the use of a single variety. This is suggested by the fact that laxation was freer in the preliminary period of our experiment when the sources of fiber were freely chosen than in most of the subsequent periods when the sources were restricted.

CLINICAL APPLICATIONS

There is no reason why the diet for constipation should not be planned with the same precision that one prescribes a diet for diabetes or for obesity. In other words the physician should be able to think in quantitative terms about fiber as he does about calories, carbohydrates, fats or proteins. Cowgill's concept of the physiologic fiber minimum should receive due recognition. The fiber content of the more important fruits and vegetables and cereals should be made more generally available to the physician.

In the accompanying tables (tables 4, 5 and 6) the fiber component is shown not only as a percentage but as it occurs in the average serving portion. By using these data the physician is now equipped to construct a diet for constipation on a quantitative basis.

According to the Cowgill standard of 100 mg of fiber per kg body weight, a man of 70 kg will normally require 7 gm of fiber daily, a woman of 55 kg will need 5.5 gm. In order to obtain this total, selection may be made in approximately equal portions, from each of the three classes of fibrous foodstuffs—fruits, vegetables and cereals. The exact procedure may be outlined as follows, bearing in mind that only bland foods should be selected at the beginning of treatment.

- 1 From the list of fruits, three varieties may be chosen, preferably one

TABLE IV
Fiber Content of Cereals and Cereal Products
(Based on Edible Portion and Average Servings)

Cereals	Amount of Average Serving		Per Cent of Fiber	Grams of Fiber per Average Serving
	Measure	Weight in Grams		
Bran, prepared	$\frac{1}{3}$ cup	20	8.5	1.70
Bran flakes	$\frac{2}{3}$ cup	30	5.1	1.53*
Corn flakes	1 cup	25	2	.05
Corn meal	$\frac{1}{2}$ cup, cooked	20 (dry)	2	.04
Cream of wheat	$\frac{1}{2}$ cup, cooked	20 (dry)	2	.04
Farina	$\frac{1}{2}$ cup, cooked	20 (dry)	2	.04
Grape nuts	$\frac{1}{4}$ cup	30	2.4	.72†
Hominy grits	$\frac{1}{2}$ cup, cooked	20 (dry)	4	.08
Noodles	$\frac{1}{2}$ cup, cooked	25 (dry)	4	.10
Oats, rolled	$\frac{1}{2}$ cup, cooked	20 (dry)	9	.18
Puffed rice	1 cup	15	1	.01
Puffed wheat	1 cup	15	1.6	.16
Rice Krispies	1 cup	30	3	.09*
Ry-Krisp	2	15	1.3	.20
Shredded wheat biscuit	1 biscuit	30	2.6	.78
Spaghetti	$\frac{1}{2}$ cup, cooked	25 (dry)	4	.10
Wheatena	$\frac{1}{2}$ cup, cooked	20 (dry)	6	.12
Wheat flakes, toasted	$\frac{2}{3}$ cup	30	1.8	.54*
Wheat krumbles	$\frac{1}{2}$ cup	30	1.9	.57
Bread				
Crackers				
Graham	2 large	15	1.5	.23
Soda	2 large	15	3	.05
Rye, whole	1 slice	30	1.2	.36
White	1 slice	30	5	.15
Whole wheat	1 slice	30	1.2	.36

The above figures for cooked cereals are based on the weight of the raw material in an average serving, the average serving being a half cup.

Unless otherwise stated, the per cent of fiber was obtained from Analyses of Common Foods Bulletin No. 373, Connecticut Agricultural Experiment Station, 1934.⁷

* Fiber value obtained from Research Laboratories, Kellogg Co., Battle Creek, Mich.

† Fiber value obtained from General Foods Corporation, New York.

for each meal. Assuming that apples, prunes and bananas are taken, it will be noted that the fiber in three average portions adds up to 2.2 gm (1.0 gm plus 0.6 gm plus 0.6 gm).

2. Four vegetables should be selected including one serving of potato (0.4 gm). If to this are added string beans (1.05 gm), spinach (0.45 gm) and asparagus (0.35 gm), the total from this source becomes 2.25 gm.

3. For the cereal foodstuffs one whole grain cereal such as shredded wheat (0.78 gm) with perhaps a slice of whole wheat bread (0.36 gm) should be taken for breakfast. At each of the other two meals two slices of bread (0.72 gm) may be used. This brings up the total for this group to 2.58 gm. For some of the bread other cereal products such as noodles, cake, pastry and certain puddings may be substituted.

TABLE V
Fiber Content of Vegetables
(Based on Edible Portion and Average Servings)

	Amount of Average Serving		Per Cent of Fiber	Grams of Fiber per Average Serving
	Measure	Weight in Grams		
Artichokes (French)	1 medium	30	3 2	96
Asparagus	6 med stalks	50	7	35
Beans				
Lima (fresh)	$\frac{1}{2}$ cup, cooked	60	1 5	90
Snap (string)	$\frac{1}{2}$ cup, cooked	75	1 4	1 05
Beets (common red)	$\frac{1}{2}$ cup, sliced	75	9	68
Beet greens	$\frac{1}{2}$ cup, cooked	75	1 4	1 05
Broccoli	1 med stalk	100	1 3	1 30
Brussel sprouts	$\frac{2}{3}$ cup	100	1 3	1 30
Cabbage	$\frac{1}{2}$ cup, raw	50	1 0	50
Carrots	$\frac{1}{2}$ cup, cooked	75	1 1	76
Cauliflower	$\frac{1}{2}$ cup, cooked	75	9	68
Celery	$\frac{1}{4}$ med stalk	40	7	28
Corn (sweet)	$\frac{1}{2}$ cup, cooked	75	8	60
Cucumbers	$\frac{1}{3}$ medium	30	5	15
Eggplant	$\frac{1}{2}$ cup, cooked	75	9	68
Kale (leaves)	$\frac{1}{2}$ cup, cooked	75	1 2	90
Kohlrabi	$\frac{1}{2}$ cup, cooked	75	1 1	76
Lettuce	$\frac{1}{4}$ med head	75	6	45
Mushrooms	$\frac{1}{2}$ cup, cooked	50	9	45
Mustard greens	$\frac{1}{2}$ cup, cooked	75	8	60
Onions	$\frac{1}{2}$ cup, cooked	75	8	60
Onions (young green)	6-8 small	50	1 8	90
Parsnips	$\frac{1}{2}$ cup, cooked	75	2 2	1 65
Peas (green shelled)	$\frac{1}{2}$ cup, cooked	75	2 2	1 65
Potatoes	$\frac{1}{2}$ cup, diced	100	4	40
Radishes	3-4 medium	30	7	21
Spinach	$\frac{1}{2}$ cup, cooked	75	6	45
Squash (summer)	$\frac{1}{8}$ squash, 5 in diam	100	5	50
Squash (winter)	2 X 2 X 1 in	100	1 4	1 40
Sweet potatoes	1 small	100	1 0	1 00
Tomatoes (red)	1 medium	100	6	60
Turnips	$\frac{1}{2}$ cup, cooked	50	1 1	55

The above figures are based on the raw weight of vegetables contained in an average cooked serving, which is a scant half cup. The percentage of fiber was obtained from Proximate Composition of Fresh Vegetables, Circular No 146, U S Department of Agriculture, by Chatfield and Adams, 1931.⁵

The foods used in the above example will give a daily total of 7.03 gm of fiber. It is to be observed that in planning this type of diet slight changes may have to be made in the patient's bill of fare: (1) more attention must be paid to the choice of fruits, vegetables and cereals, (2) fruits will usually have to be substituted for the common non-fibrous desserts, such as ice cream, custard and gelatin preparations.

As regards the particular fibrous foodstuffs to be recommended, it need hardly be pointed out that clinical judgment should be the guide in practice. Common experience as well as individual idiosyncrasies should always be respected. Just because a certain fruit or vegetable possesses much fiber is

TABLE VI
Fiber Content of Fruits
(Based on Edible Portion and Average Servings)

	Amount of Average Serving		Per Cent of Fiber	Grams of Fiber per Average Serving
	Measure	Weight in Grams		
Apples (all varieties)	1 small	100	1.0	1.0
Apricots (without pits)	3 medium	100	.6	.6
Bananas	1 medium	100	.6	.6
Blackberries	1 cup	100	4.1	4.1
Blueberries	$\frac{1}{2}$ cup	100	1.2	1.2
Cherries	$\frac{1}{2}$ cup, stoned	100	.3	.3
Cranberries	$\frac{1}{2}$ cup, cooked	30	1.4	.42
Figs (fresh)	2-3 medium	100	1.7	1.7
Figs (dried)*	2-3 medium	75	2.4	1.8
Grapefruit	$\frac{1}{2}$ medium	100	.3	.3
Grapes (American type)	1 med bunch	100	.5	.5
Huckleberries	$\frac{1}{2}$ cup	100	1.2	1.2
Muskmelons or cantaloupe	$\frac{1}{3}$ medium	100	.7	.7
Oranges	1 small	100	.6	.6
Peaches	1 medium	100	.6	.6
Pears	1 medium	100	1.4	1.4
Pineapples	$\frac{1}{2}$ cup, diced	75	.4	.3
Plums	4-5	100	.5	.5
Prunes (fresh)	4-5	100	.5	.5
Prunes (dried)†	3-6	30	1.8	.6
Raspberries (black)	1 cup, scant	100	3.5	3.5
Raspberries (red)	1 cup, scant	100	2.8	2.8
Rhubarb	$\frac{1}{2}$ cup, cooked	75	.7	.52
Strawberries	1 cup, scant	100	1.2	1.2
Tangerines	1 large	100	1.0	1.0
Watermelon	1 med serving	150	.6	.9

Unless otherwise stated, the per cent of fiber was obtained from Proximate Composition of Fresh Fruits, Circular No. 50, U. S. Department of Agriculture, by Chatfield and McLaughlin, 1931.⁶

* Calculated from the fresh fruit

† Fiber value obtained from California Dried Fruit Research Institute, San Francisco

not in itself a sufficient reason for its recommendation. It is not very likely, for example, that patients able to tolerate corn, cabbage, baked beans and rough berries will consult a physician for the relief of constipation. Von Noorden was very careful to point out that only a few of the simpler fibrous foods should be used at the beginning of treatment, and that these should be continued in full doses until regular function is well established. It is only after this is accomplished that more stimulating foods may be added. Every effort should be made to avoid colic, distention and other evidences of irritation, *since the resulting spasm may serve to increase the fecal stasis*.

In any regimen for the treatment of constipation adequate water intake is essential to supply the means by which the fruit and vegetable pectins and galactans soften the feces. A daily minimum of four to six glasses (1000 to 1500 cc) is necessary, water taken immediately on arising being espe-

cially beneficial. An increased fat intake is also desirable but this has limitations in practice. Its chief application is in undernourished subjects where it is best taken in the form of butter, in amounts up to $\frac{1}{4}$ lb daily. Olive oil (1 oz. two to three times a day) as such, or as "cocktail" with tomato juice or orange juice, is acceptable to some people.

A few suggestions in the practical use of fruits may be of interest. Our experience indicates that the addition of fruit in the amount of 33 mg of fiber per kg. to an "average" diet, containing approximately 66 mg per kg. of fiber from other sources, should relieve constipation in many, if not most, simple cases. As already explained, this amounts, for an average man, to a little over 7 gm of fiber per day. In obstinate cases of constipation, however, the amount of fruit fiber may have to be increased considerably, additional fruit being taken between meals if necessary.

The discovery of an active principle in prunes suggests that certain fruits may possess special cathartic properties in addition to their fiber-acid-sugar content. However, our experiment fails to show outstanding superiority for prunes because only five out of our nine subjects rated them first in laxation and two reported them least effective as compared with the other two fruits studied. In any event further investigation in this direction is desirable. Prune juice is said to contain the same active principle as the whole fruit. It may therefore be more widely used as a breakfast drink either instead of or in addition to the citrous fruit juices.

Cooked apples may be substituted for the raw. Bananas may be served in any way desired, but if eaten raw they must be ripe since the unconverted starch may cause "indigestion". The criteria of ripeness are that the skin is entirely yellow and generously flecked with brown and that the pulp has softened. At this stage practically all the starch is converted into easily digested fruit sugars. Attention should be called to the fact that in the ripening process the tip of the fruit is the last portion to show traces of green color. It may therefore be used as an indicator of fitness for consumption. Obviously, it is not correct to cut off the green portion as is done in some households, and offer the rest of the unripe fruit to be eaten.

SUMMARY AND CONCLUSIONS

1. An adequate fiber intake is important in the dietetic treatment of constipation. Fiber is supplied by three classes of foodstuffs,—fruits, vegetables and cereals.

2. The relative laxative value of typical fruits was studied in human subjects on a fiber-equivalent basis. Previous work showing that the laxative effect of a diet depends largely on its fiber content was confirmed and the value of such typical fruits was demonstrated. Although prunes were found to be generally more laxative than apples or bananas, yet each of the latter proved more effective in individual cases. There is reason to believe that bananas are of special value in constipation associated with colonic instability.

3 Tables are furnished showing the fiber content of the common fruits, vegetables, and cereals, in per cent by weight and in amount per portion. With the aid of such data constipation diets may be planned on a quantitative basis.

4 In the selection of fibrous foods only bland articles should be used at the beginning of treatment because rough foodstuffs may provoke bowel irritation with resulting spasm and increase in constipation.

5 For the relief of many, if not most cases of simple constipation ordinary servings of fruit should be taken three times daily, preferably as desserts. It is suggested that the daily use of approximately 2 gm of fruit fiber in addition to the "average" diet, containing four vegetables and some whole grain foodstuffs, suffices in such cases. This amount would be supplied for example by six prunes, one banana and one medium-sized apple. In more obstinate cases proportionately larger intake would be needed.

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THE OCCURRENCE OF CORONARY THROMBOSIS IN YOUNG INDIVIDUALS¹

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CORONARY thrombosis in young adults has been generally considered of rare occurrence. There is much statistical evidence to support this opinion. Levine and Brown¹ in their classical monograph on coronary thrombosis reported 145 cases with an average age of 57.8 years. There were only three cases in this group under the age of 40, and none was younger than 35. The report of Connor and Holt² included 287 cases, 20 being under 40 years of age and only two under 35. Many other articles on this subject give similar statistical data as to age distribution.

Recently, however, reports have appeared in the literature indicating that coronary thrombosis is not as strictly limited to age periods beyond 40 as was previously supposed. Leary,³ in an interesting study dealing with the pathology of coronary arteriosclerosis and its relationship to the cholesterol metabolism, includes reports on the postmortem findings in eight cases of coronary thrombosis occurring in individuals under 40 years of age, five of whom were under 35. White⁴ has recently reviewed 14 cases of coronary thrombosis in individuals under the age of 40. Smith and Bartels⁵ reviewed isolated case reports in the literature and were able to collect 20 proved cases in patients 40 years of age or younger, and to this group they have added two cases of their own in which the ages of the patients were 35 and 36 years respectively.

That coronary thrombosis may occur with surprising frequency in younger individuals is further emphasized by the recent high incidence of such an occurrence at the University Hospital, Ann Arbor, Michigan. Seven cases occurring in patients 35 years of age or under have been observed in this clinic during the four year period from 1931 to 1935. This group constitutes 6.1 per cent of the 114 proved cases of coronary thrombosis recorded in the files of the University Hospital.

CASE REPORTS

Case 1 L. G., a Jewish male student of 23 years, had experienced, during a period of 10 weeks prior to his admission to the University Hospital, three attacks of severe, grasping, substernal pain, radiating to the left arm, and relieved only by narcotics. Prostration, profuse perspiration and dyspnea were associated with these attacks. His past history and family history were negative. The physical examination on admission was negative. The blood pressure was systolic 122 mm. Hg and diastolic 70. The routine urine and blood examinations, including the Kahn reaction, were negative. The standard electrocardiogram taken shortly after admission is reproduced in figure 1 A. The large Q-wave with a small R-wave in Lead I,

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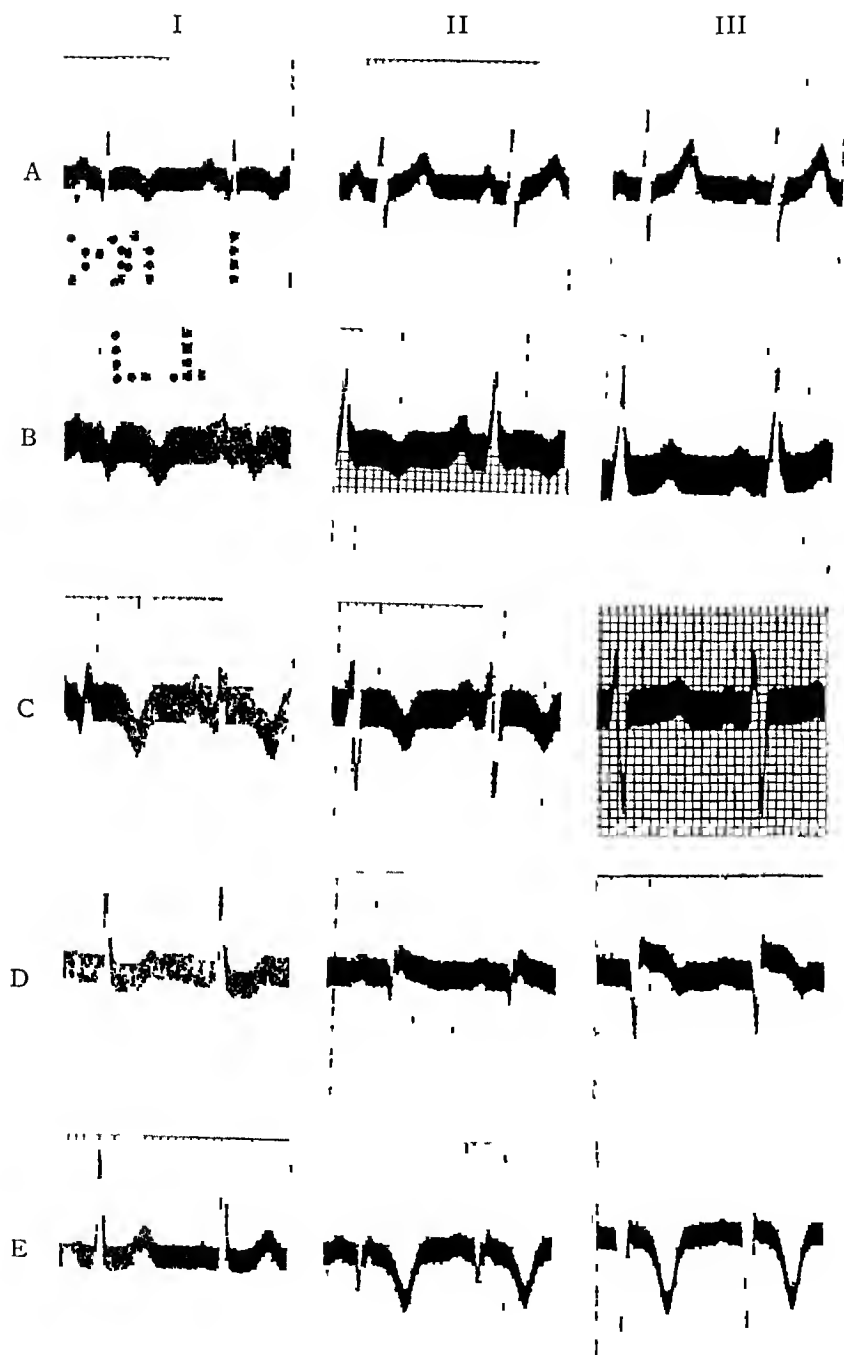


FIG 1

- A*—Case 1, standard electrocardiogram showing large Q-waves and inverted T-waves in Lead I
B—Case 2, standard electrocardiogram showing large Q-waves in Lead I and inverted T-waves in Leads I and II
C—Case 3, standard electrocardiogram showing large Q-waves in Lead I and inverted T-waves in Leads I and II
D—Case 4, standard electrocardiogram, taken within a few hours of the onset of symptoms of coronary occlusion, showing large Q-waves in Leads II and III, depression of the S-T segment in Lead I and elevation of the S-T segment in Leads II and III
E—Case 4, standard electrocardiogram, taken 22 days after acute coronary occlusion, showing large Q-waves and markedly inverted T-waves in Leads II and III

together with the sharply inverted T_1 , confirmed the clinical diagnosis of coronary occlusion, and pointed to an anterior location of the infarct. The precordial electrocardiogram (figure 2) provided evidence of an extensive anterior infarct.

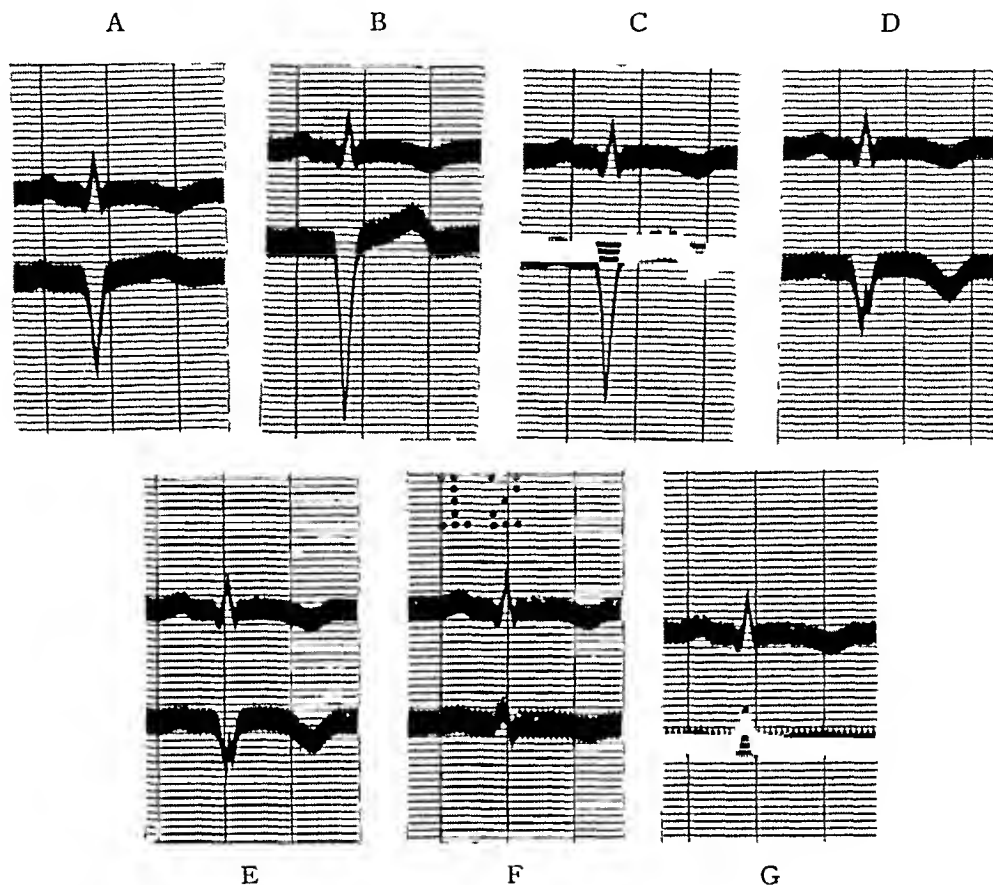


FIG 2 Case 1, precordial electrocardiogram (lower curve) taken simultaneously with standard Lead I (upper curve) according to the method of Wilson, Johnston, Macleod and Barker.⁸ The leads were so connected that relative negativity of the exploring electrode is represented by a downstroke.

- A—5th rib at right edge of sternum
- B—5th rib at left edge of sternum
- C—5th i c s mid-way between sternum and left mid-clavicular line
- D—5th i c s at mid-clavicular line
- E—5th i c s at left nipple line (2 cm to left of D)
- F—6th rib in left anterior axillary line
- G—6th i c s in left mid-axillary line

The normal initial upstroke is absent in A, B, C, D and E, a finding indicative of myocardial infarction. Note also the T-wave changes in C, D and E.

Case 2 G K, a carpenter, aged 33, had been in good health until 10 months before admission when he had begun to notice epigastric soreness and dyspnea brought on by marked exertion and relieved by rest. Six weeks before admission, following a heavy meal, a severe attack of epigastric pain associated with vomiting, dyspnea, and palpitation had necessitated his admission to a hospital where his temperature was found to be 102.6° F and the white blood cell count 21,600. Following this attack, anginal symptoms had been induced by less exertion than previously. The past history and family history were negative. The physical examination on

admission to the University Hospital was entirely negative. The blood pressure was systolic 115 mm Hg and diastolic 72. The peripheral arteries were soft. The blood Kahn reaction, urine and routine blood examinations were negative. An orthodiagram showed the heart to be normal in size. There was slight widening of the base of the aorta. The standard electrocardiogram (figure 1 B) showed a large Q-wave in Lead I and sharply inverted T-waves in Leads I and II. These findings were considered diagnostic of an anterior wall infarct. The precordial electrocardiogram (figure 3) confirmed this diagnosis and demonstrated the extensive distribution of the area of infarction.

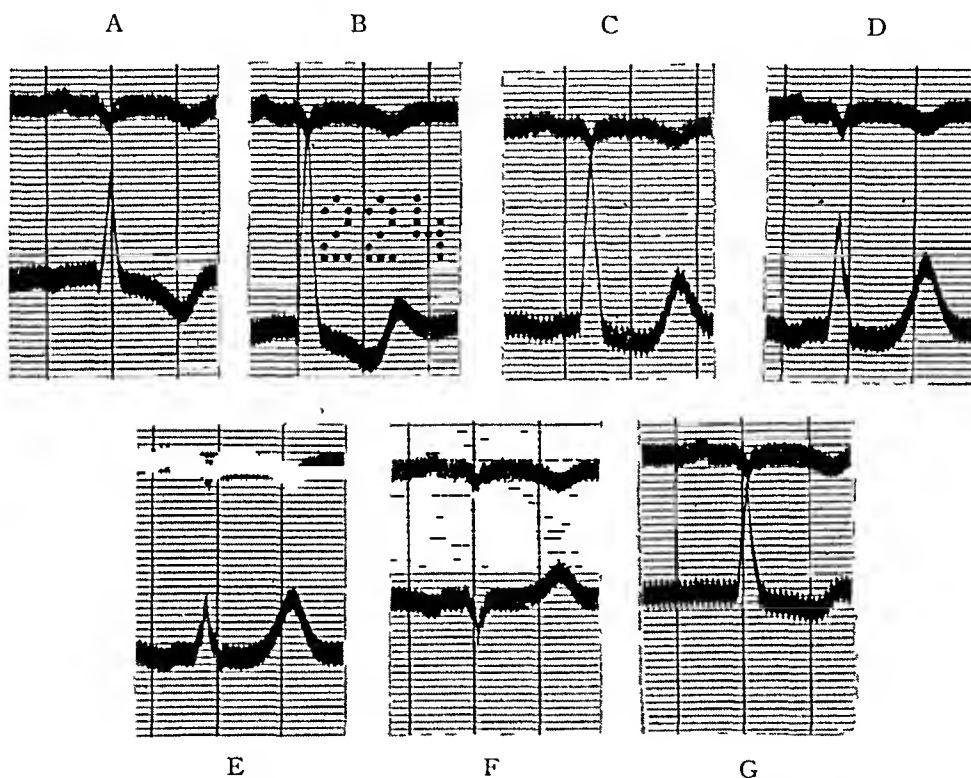


FIG 3 *Case 2*, precordial electrocardiogram taken in the same manner as in case 1 (figure 2) except that the leads were so connected that relative negativity of the exploring electrode is represented by an upstroke.

A—5th rib at right edge of sternum

B—5th rib at left edge of sternum

C—5th ICS mid-way from sternum to mid-clavicular line

D—5th ICS in left mid-clavicular line

E—6th rib, left anterior axillary line

F—7th rib, left mid-axillary line

G—3d rib, left mid-clavicular line

The normal initial downstroke is absent in C, D, E and G, a finding indicative of myocardial infarction. Note also the abnormal T-waves in C, D, E and F.

The patient was discharged greatly improved after a six weeks' period of bed rest. No subsequent information is available.

Case 3 J H, a tool grinder, aged 31 years, had noted mild precordial pain on exertion or following excessive drinking over a period of two years. Two weeks before admission, he had experienced an attack of severe precordial pain radiating to the neck and down the left arm. A second attack occurred four days later and

was associated with fever, palpitation and dyspnea. The past history was negative except for three attacks of gonorrhea. He denied luetic infection. He had been married 13 years and had one child living and well. There had been no miscarriages or still-births. He had been a heavy drinker and had used tobacco to excess. The family history was negative. The physical examination was entirely negative. The blood pressure was systolic 120 mm Hg and diastolic 70. The peripheral arteries were soft. The retinal vessels showed no abnormalities. The blood Kahn reaction, urine and routine blood examinations were negative. The standard electrocardiogram (figure 1 C), a typical curve of the Q_1T_1 type, confirmed the clinical diagnosis of coronary occlusion, as did the precordial electrocardiogram, which demonstrated a large anterior infarct.

Case 4 R M, an auto mechanic, aged 35 years, had been in good health until one and one-half years before admission to the hospital when he had experienced severe precordial pain of six hours' duration. Except for some cardiac irregularity he had felt well following this attack until five weeks before admission. At this time another attack of severe precordial pain occurred and lasted for nine hours. Following this second attack, the patient had been unable to return to work because of dyspnea and precordial discomfort induced by exertion. The past history was negative. The family history was incomplete. Physical examination showed marked cardiac enlargement and signs of congestive failure. The blood pressure was 142 mm Hg systolic and 100 diastolic. The blood Kahn reaction, urine and routine blood examinations were negative. A roentgenogram of the chest showed moderate cardiac enlargement and passive congestion of the lungs. The standard electrocardiogram showed a large Q-wave and a small R deflection in Lead I with a sharply inverted T_1 , findings indicative of infarction of the anterior wall of the heart. Following a period of treatment, the patient was discharged and no later information is available.

Case 5 I T, a Jewish male of 33 years, had suffered four attacks of severe, prolonged substernal pain over an eight year period prior to his admission to the hospital. Since the last attack three years previously he had complained of dyspnea on exertion and weakness. He had been a known diabetic since his first attack. The past history and family history were not recorded. Physical examination showed slight enlargement of the heart, but no other cardiac abnormality was noted. The blood pressure was 120 mm Hg systolic and 75 diastolic. The brachial arteries were soft. The remainder of the physical examination was negative. The blood Kahn reaction and routine blood examination were negative. The urine gave a three plus reaction to Benedict's solution, but was otherwise negative. The standard electrocardiogram showed marked left axis deviation with large Q-waves in Lead I. The patient's diabetes was readily controlled on a diet yielding 90 grams of available glucose with 10 units of insulin daily. He was seen nine months later, at which time he reported marked symptomatic improvement. He had had no further chest pain.

Case 6 J K, a 31 year old mechanic, had been well until five months before observation at which time he had begun to experience attacks of epigastric pain associated with dyspnea, nausea and vomiting. The past history was entirely negative. He had been married 11 years and had one child living and well. His wife's first pregnancy had resulted in a miscarriage. The family history was negative. The physical examination on admission revealed pupils that reacted sluggishly to light, but well in accommodation. The heart was enlarged, but was otherwise negative. The blood pressure was 110 mm Hg systolic and 80 diastolic. The liver edge was palpable at the level of the umbilicus and was smooth and tender. The remainder of the examination was negative. The blood Kahn reaction and routine blood examinations were negative. The urine gave a three plus reaction for albumin and contained 15 white blood cells per high power field, and was otherwise negative. A

roentgenogram of the chest showed gross left cardiac enlargement and widening of the base of the aortic arch. The standard electrocardiogram showed high grade intraventricular block (QRS interval 0.13 second), large Q-waves in Lead I, inverted T-waves in Lead I, and large, broad S-waves in Leads II and III. The patient became markedly jaundiced shortly after admission to the hospital and his general condition grew progressively worse. Death occurred in two weeks. Postmortem examination revealed a localized syphilitic arteritis at the mouth of the left coronary artery with a nearly complete occlusion of the anterior descending branch. There was a myocardial infarct at the apex extending up from the apex 9 cm. on the anterior wall and 4 cm. on the posterior wall. Other findings included hemorrhagic infarction of the lungs, nutmeg liver, slight arteriosclerotic nephropathy, and acute exacerbation of chronic passive congestion of all organs. The postmortem blood Kahn reaction was positive.

Case 7 J. W., a 33 year old metal polisher, was admitted to the University Hospital with anasarca of one month's duration. Four abscessed teeth had been removed one month before the onset of the generalized edematous condition. The patient had had whooping cough, diphtheria, tonsillitis, and possibly scarlet fever in childhood. The family history was negative. Physical examination showed considerable pallor. The tonsils were medium sized and did not appear infected. The eye-grounds appeared normal. The cardiac examination was negative. The blood pressure was systolic 190 and diastolic 110. There were signs of fluid at both lung bases and in the abdomen. The legs were edematous. The blood Kahn reaction and routine blood examinations were negative. The urine showed four plus albumin, and several red and white blood cells per high power field, and 10-30 casts per low power field. The blood non-protein-nitrogen was 37.5 mg. per cent. Five days following admission, while having his back rubbed, the patient developed severe substernal pain. This pain lasted five days and was relieved only by morphine. There was considerable dyspnea with the attack. The temperature and white blood cell count were elevated. A series of electrocardiograms showed changes characteristic of infarction of the posterior wall of the heart. Two of the electrocardiograms have been selected and are reproduced in figure 1 D and E. Several months after the attack of coronary occlusion, and while still in the hospital, the patient developed severe pleuritic pain associated with fever. Death occurred one week later. Postmortem examination showed an occlusion of the right coronary artery 3 cm. from its origin. There was extensive infarction of the posterior wall of both ventricles extending into the septum. The lungs showed hemorrhagic purulent pneumonia. There was an early subacute glomerulo-tubular nephritis with lipoidosis of the tubular epithelium.

COMMENT

Coronary occlusion in older individuals is ordinarily the result of degenerative changes associated with advancing age. What factors were responsible for the premature coronary changes in the patients above described is an interesting and important question. Factors of recognized importance are syphilitic infection, hypertension and diabetes. In four of these patients the explanation may be wholly or partly on the basis of one or the other of these factors. In two of them, cases 4 and 7, hypertension undoubtedly played a part in the development of the coronary condition. Diabetes may be held partly responsible for the premature occurrence of severe coronary disease in case 5. In one patient, case 6, syphilitic infection involving the mouth of the left coronary artery was responsible for the oc-

clusion and resultant infarction of the myocardium. The finding of infarction of the myocardium in this patient is emphasized inasmuch as it is a rare complication following the occlusion of an orifice of a coronary artery or stenosis of one or both orifices by the syphilitic process (Von Glahn ⁶).

There remain three patients (cases 1, 2 and 3) in which the etiological factors above mentioned were entirely lacking. The basis for the premature coronary disease in them remains obscure. An attempt has previously been made to explain cases of this type on the basis of an inherited susceptibility to arterial degeneration. Musser and Barton ⁷ have advanced the hypothesis that there are two distinct expressions of coronary disease. One is observed in elderly individuals, representing largely the effect of senescence. The other is said to be observed in younger men with a familial tendency to coronary disease. A review of the family histories in the three cases under consideration reveals no familial tendency.

It is of interest in reviewing the entire group of seven cases to note that all the patients were males, none was overweight, none was engaged in a professional occupation and in none, except the patients with nephritis and syphilis, did infection appear to play a part. Five of the seven patients were engaged in occupations requiring hard labor. Only one patient (case 3) reported having used tobacco to excess.

The mortality of the acute attack of coronary thrombosis in these cases was unusually low. Five of the seven cases survived their attacks by at least six weeks. Subsequent information is not available except in case 5, in which case the first attack had been survived eight years.

SUMMARY

Coronary thrombosis in young adults, although generally considered to be a rare condition, may occur with surprising frequency. Seven cases in patients ranging in age from 22 to 35 are reported.

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THE ESTIMATION OF CARDIAC FUNCTION BY SIMPLE CLINICAL METHODS *

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THE problem of determining the functional impairment, or conversely the cardiac reserve of ambulatory cardiac patients has always been a baffling one. Even with the use of all our modern laboratory adjuncts—the fluoroscope, roentgen-ray measurements of the heart, and lastly the electrocardiogram, in addition to all available clinical methods, one is often at a loss to decide just where in the scale of impairment of cardiovascular function a particular patient belongs. This difficulty of course arises chiefly in the case of the strictly ambulatory cardiac patient, since those patients who show evidences of *decompensation* either at rest or after moderate activity all plainly belong to Class III of the American Heart Association's functional classification.

It is in attempting to differentiate between Class I patients, "those with organic heart disease manifesting no significant disability for the ordinary activities," and Class II A patients, "those manifesting ability to perform with slight impairment," and between the latter Class and Class II B patients, "those with considerable impairment of ordinary activity," that one is confronted with many pitfalls. For the criteria on which we are prone to base our differentiation are in the main purely subjective symptoms, and as Libman has so ably pointed out, the sensitivity (and consequently reactivity) of different individuals to noxious and painful stimuli is extremely variable. The use of our recently acquired laboratory adjuncts to cardiac diagnosis often (though certainly not always) helps us to determine objectively to some degree how much actual disease is masked or magnified under a cloud of subjective complaints.

But these measures are usually not available to the average medical examiner, and he must form his judgment as to the cardiac efficiency of his patient solely on the information obtained by his eyes, hands, ears and a critical mind. Yet upon this judgment must be based prognostic determinations as to the insurability of the patient, disability estimates for compensation purposes, and last but not least therapeutic decisions. Shall he tell the stolid unsuspecting laborer before him, in whom he has found a well-defined organic murmur, that he is a "cardiac" and must change his occupation and otherwise lead a restricted and closely regulated life, or shall he casually inform him that the examination has revealed a "slight leak" which is of little importance, and requires him to make little or no change in his mode of living, beyond observing the ordinary precaution of having a

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periodic medical examination? The fallibility of basing such decisions merely on the character of the murmur is too evident to require elaboration here. It is the purpose of this paper to show whether, and if so, to how great a degree, the facts elicited on an ordinary clinical physical examination can be relied upon in estimating the degree of cardiac disability in these types of cases. This will be done by showing the amount of correlation existing between certain readily observable clinical data and the evidences of myocardial damage furnished by the laboratory.

The writer is well aware that various and numerous so-called "effort" and "cardiac function" tests have been put forward in the past. Many of these are not suitable in that they do not represent the ordinary activities of the individual's everyday life (such are spirometer, flarimeter, etc.). All of them are deficient in that no two individuals can be expected to exert the same degree of effort in performing the same tasks. One will walk up and down the prescribed number of steps with vigor, another in an ordinary manner, and a third gingerly or lackadaisically. Similarly in hopping tests, in spite of explicit directions, one will barely more than timidly raise his heels off the floor the required number of times, another will more or less closely approximate the "50 hops—3 inches off the floor—at one second intervals," while a third will leap with great abandon as high as he can off the floor until he is abruptly restrained. The writer proposes no new variation of the exercise tests, as he believes the above sources of inaccuracies are in the main unavoidable. However, since a quantitative equality of the amount of exertion in various individuals cannot be attained, we have tried to avoid as much as possible a quantitative comparison of the results. Instead we have stressed the qualitative relations of the cardiorespiratory adjustment to exercise,—that is, not "exactly how much" the pulse and respiration have increased after exercise, but rather "in what manner" the proportion between pulse and respiration has varied after exercise as compared with the proportion before exercise.

Methods In these studies the following technic was closely followed. The patient's pulse and respiration were taken while he was standing at rest. After the patient had been still long enough for stable rates to be established (generally after a wait of 15 to 30 seconds), the cardiac apex rate was counted (with the stethoscope) for 10 seconds, and immediately thereafter (with the stethoscope still on the chest) the respirations were counted for 15 seconds. These short periods of counting were used because experience showed that the maximal rate changes generally occur very rapidly and subside very rapidly. The patient was then asked to hop 50 times (25 times on each foot), and immediately thereafter the pulse and respiratory rates were taken in exactly the same manner. The auscultatory method of counting both the rates was used exclusively as it was found to be more accurate than the palpatory method, and because it did not interfere with the simultaneous observation (on the "second" dial of a watch) of the elapsed time.

intervals, as a visual method would have done. Since all the observations were made by the same examiner, individual differences in the technic were reduced to a minimum. At this point it may be stated that "sitting resting rates" and "rates three minutes after," and in some cases "rates two minutes after" the completion of the exercise were also taken routinely on all cases. These data, however, will not be considered in this study as it was soon found that there were no significant differences in these factors in many cases of even obviously greatly differing functional cardiac capacities. (For example, a case of marked valvular disease with evident functional impairment was quite as apt to show no elevation of the pulse and respiration three minutes after exercise, as was a case with no cardiac lesion.) Although, as hinted above, 50 hops were routinely asked for, in certain cases more or less were required as it was felt that only exercise sufficient to cause manifestly increased respiratory effort would serve to bring out the qualitative differences mentioned in the previous paragraph.

Why were the criteria just indicated, namely, tachypnea and the pulse-respiratory ratio after exercise, chosen to the exclusion of others? Simply because other criteria are not readily measurable from a practical standpoint. This criticism applies to the usually stressed "dyspnea" or "shortness of breath" and equally to "cyanosis" which necessarily must be subjectively estimated by the examiner. The other definite clinical criteria of impaired cardiac function, namely edema, hepatic and pulmonary congestion, marked cardiac irregularities such as fibrillation, and of course extreme dyspnea and cyanosis, as well as characteristic angina, all are found only in cases that offer no problem for functional classification—they all belong definitely in Class II B. Such cases not only do not usually require a cardiac function test for the demonstration of their disability, but actually may be hazardous subjects to put through such an ordeal.

Clinical Material The material on which these studies were made comprised ambulatory out-patients examined by the writer, consecutively, over an 18 months' period (from September 1931 to May 1933), at the Veterans' Facility at Lyons, New Jersey. They were all veterans, being examined in regard to claims for disability compensation, disability allowance, or insurance purposes. The great majority were veterans of the World War, —the remainder veterans of the Spanish American War and allied expeditions. Data for this study were collected on 209 cardiac cases, and on 101 non-cardiac controls. A substantial majority of the patients had been previously examined by other Veterans' Bureau examiners, and in the occasional instance where there existed a significant discrepancy between the findings in the earlier and in the later examinations, no change was made in the diagnosis unless the later findings were confirmed by a consultant examiner (Dr J. E. Maloney). Occasional patients returned for re-examination during the 18 months' period of the study thus permitting a personal checking of the earlier findings. The ages of the patients under

consideration ranged from a minimum of 29 years for the World War veterans to a maximum of 64 years for the Spanish War veterans. Although the clinical impressions which are the result of this study were derived as a result of the observation of all the 209 cardiac cases and the 101 non-cardiac controls, the statistical corroboration of these impressions will be based only on those 65 cases that were worked up completely from a laboratory as well as clinical angle, viz, those cases in which complete electrocardiographic and roentgenological studies were made in addition to the usual routine clinical physical examination and urinalysis. The following table will indicate the pathologic-anatomical division of the material. It will be noted that the completely worked up cases are listed under the heading, "Complete Data Cases."

TABLE I

Key Letters	Pathologico-Anatomical Type	Total Number of Cases	Number of "Complete Data Cases"	Average Age
Rm	Rheumatic heart disease, typical mitral stenosis and regurgitation	52	18	38.5
Ra	Rheumatic heart disease, aortic valvulitis (stenosis or regurgitation or both)	15	4	42.3
Ra and m	Rheumatic heart disease, combined aortic and mitral valvulitis	38	10	35.3
M	Pure mitral regurgitation	26	8	39.9
H	Hypertensive heart disease	41	6	41
A	Arteriosclerotic heart disease	14	6	44.2
L	Luetic heart disease	7	3	36.3
E	Emphysematous heart disease	2	2	53.5
F	"Functional" heart cases	14	5	42.2
	<i>Totals</i>	209	62	
X	Non-cardiac controls	101	3	

It should be explained that Class "M"—"Pure Mitral Regurgitation"—is not to be considered a specific pathological-anatomical group. Undoubtedly a large proportion of these cases correctly belongs under the "Rheumatic" heading. However, since it is impossible to obtain an accurate history with this type of patient, the writer prefers to list only those cases with typical auscultatory and palpatory findings under the rheumatic classification. The "functional" group is also a rather miscellaneous one and includes such diagnosis as "essential tachycardia", "neurocirculatory asthenia", "tachycardia with severe diabetes", "myxedema heart", "alcoholic tachycardia", "pseudo-angina pectoris," etc.

The average age of 90 non-cardiac controls was 38.4 years, and of 54 "Complete Data" cardiac cases—39.5 years.

Results As these studies progressed, the writer began to feel that a triad of clinical signs often appearing after ordinary exercise, could be taken as fairly reliable indices of cardio-respiratory embarrassment, and inferentially,

in those cases in which no respiratory disease or other obvious cause of increased pulse or respiratory rate was detectable, the occurrence of these signs pointed toward the existence of organic heart disease with definitely impaired function. These signs were (1) Tachypnea, an increase of the respiratory rate immediately after exercise to 24 or more per minute, (2) a "paradoxical pulse-respiratory ratio," i.e., a ratio of pulse rate to respiratory rate which is not greater after exercise than before, (3) a diminished pulse lability as indicated by the presence of a pulse/respiratory ratio after exercise which is less than a certain critical minimum norm determined for this age group to be 4.5. The first of these signs was found to be the one most frequently observed, but the third sign is probably that of greatest significance.

In order to show how the "critical" norm for the pulse/respiratory ratio was determined it will be necessary to consider first the results obtained in the study of the 101 control cases. These comprised 101 veterans belonging to an essentially similar age group as our cardiac cases, but suffering from no detectable cardiac or respiratory disease. These cases were all put through the same exercise routine described above and the same pulse and respiratory readings were taken. Of these 101 cases, 74 showed no tachypnea after the prescribed exercise. On the other hand 27 control cases did show tachypnea (a post-exercise respiratory rate of 24 or more). Since cardiac and respiratory disease were presumably ruled out in these cases, it is necessary to explain this tachypnea on the basis of so-called "nervous" or "emotional" factors. Apparently by far the commonest evident etiological factor was the presence of physical disabilities that were obviously inducive of pain when the prescribed exercise was performed. Such disabilities varied from common conditions such as painful flat or weak feet, herniae, sacro-iliac disease, various grades of arthritis particularly of the lower extremities, to comparatively rare disabilities such as thromboangiitis obliterans. All but some five of these control cases showing tachypnea presented lesions that would be patently pain provoking under the prescribed exercise. Only these few then need be explained on "nervous factors." The writer is so impressed by the frequency of tachypnea in painful conditions, that he believes the presence or absence of an increased respiratory rate may be taken as a fairly reliable objective index of the presence of pain in cases where malingering may be suspected.

To return to our main thesis, however, we found that the average post-exercise pulse-respiratory ratio after exercise for the 74 control cases that did not exhibit tachypnea was 6.5 while for the 27 control cases that did show tachypnea it was 4.36. Accordingly, the writer feels that in our cardiac group (which has approximately the same age distribution), where no obvious respiratory, or painful somatic, or "nervous" (such as hyperthyroidism) etiological factors are present, it is permissible to assume that a

TABLE IIA
Organic Cardiac Cases Manifesting Tachypnea after Exercise
(24 plus/minute)

Case Key No	Post exercise Pulse/Respiratory Rate	Post exercise Pulse/Respiratory Ratio (P/R)	X-Ray Findings (Cardiothoracic Ratio)	Electrocardiographic Findings					Laboratory Pathology Factor and Remarks (LPF)
				Dura- tion "P"	Dura- tion "PR"	Changes of "QRS" (R Base Width)	"T" Wave Changes	Axis Devia- tion	
Rm 7	132-24	5.5	13 2/28 6	08	16	06	—	Marked RAD	LPF-I
Rm 38	132-24	5.5	13 8/30	10	20	05	—	RAD	LPF-I
Rm 54	114-24	4.75	12 5/29 5	08	16	06	—	—	LPF-0
Rm 60	114-24	4.75	12 5/29 5	08	16	07	—	RAD	LPF-II
Rm 65	174-24	7.33	10/28 5	08	16	06	—	—	LPF-0
Ra & m 22	108-24	4.5*	14 5/29	10	20	07	T ₃ neg	Marked RAD	LPF-II
Ra & m 24	126-24	5.25	13 9/31	09	16	04	T ₁ flat T ₂	—	LPF-I
Ra & m 25	168-24	7	13 3/30	08	16	04	T ₃ neg	—	LPF-IV
Ra & m 28	108-24	4.5*	16/30 5	12	20	07	T ₁ & 3 cone	LAD	LPF-IV
Ra & m 30	114-30	Resting 3.9 > 3.8*	12 5/27 2	09	16	09	—	LAD	LPF-II
Rm 32	138-24	Resting 6.44 > 5.75	13 2/26	08	16	04	T ₃ neg	—	B P 202/130 LPF-I
Rm 34	126-32	Resting 5.63 > 3.94*	14/29 5 full left border	08	16	05	—	Slight RAD	LPF-I
Rm 37	162-30	5.4	12 9/29 5	15	20	14	T ₂ , T ₃ neg	RAD	LPF-IV Shows rt bundle branch block
Ra 9	114-28	Resting 4 = 4*	15/31	08	16	05	T ₁ neg	LAD	LPF-II
Ra 13	120-24	Resting 5 = 5	13 5/27 2	08	16	06	—	—	LPF-0
Ra 15	144-24	6	13 5/30	08	16	06	T ₃ neg	RAD	LPF-I

TABLE IIA—Continued

Case Key No	Post exercise Pulse/Respiratory Rate	Post-exercise Pulse/Respiratory Ratio (P/R)	X-Ray Findings (Cardiothoracic Ratio)	Electrocardiographic Findings					Laboratory Pathology Factor and Remarks (LPF)
				Duration "P"	Duration "PR"	Changes of "QRS" (R Base Width)	"T" Wave Changes	Axis Deviation	
M 12	138—24	Resting 6 > 5 75	11 8/28 6	08	17	05	—	RAD	LPF—I
M 13	114—24	4 75	11 2/28 5	08	16	06	—	LAD	LPF—I
M 16	144—24	6	13 6/32 5	07	16	06	—	—	LPF—0
H 14	144—33 (after 26 hops)	Resting 4 4 > 4 37*	13 9/32	14	20	05	—	—	LPF—I
L 4	120—30	4*	18/30	08	16	06	T ₁ neg	—	B P 206/106
A 10	124—36	3 44*	13 5/32	12	24	05	Coronary T ₃	LAD	LPF—II B P 200/55
A 11	114—24	Resting 4 75 = 4 75	14/31 5	08	16	08	Flat T ₁ , Diphasic T ₂ , Neg T ₃	—	LPF—IV Low voltage
A 12	96—24	4*	15/30 5	12	24	12	Coronary T ₃	—	LPF—I
								Poor EMF Notched QRS	LPF—V
A 14	138—27	Resting 8 > 5 1	11 8/29	10	20	06	Flat T ₁ , T ₂ , T ₃	—	LPF—II
E 1	90—28	Resting 3 3 > 3 2*	12 5/28 5	10	16	06	—	—	LPF—0, shows mod cyanosis at rest
E 2	144—24	Resting 6 = 6	11 9/31	14	24	08	—	—	LPF—II B P 198/118

KEY TO TABLE

- 1 Reduced pulse lability is indicated by star (*) after P/R ratio
- 2 Paradoxical P/R ratio is indicated by resting being listed before post-exercise P/R ratio
- 3 Definitely pathological laboratory findings are italicized. Thus each italicized item represents a "unit" of laboratory pathology
- 4 The pathologico-anatomical diagnosis in each case may be ascertained by referring to the key letters listed in table 1

pulse/respiratory ratio of similar reduced magnitude (i.e. 4.5 or less), is indicative of impaired cardiac function

We shall now see how our laboratory studies checked up our clinical impressions. In this connection it is pertinent to emphasize that all the roentgen-ray and electrocardiographic readings were made by another physician-specialist (Dr R. S. E. Murray) who had no clinical contact with the patients, and so could not conceivably be influenced in interpreting the significance of doubtful or borderline plates or graphs. Before proceeding further we wish to mention all those laboratory findings which were considered definitely pathological. Roentgen-ray findings were considered definitely pathological only when the transverse diameter of the heart equalled or exceeded one-half the trans-thoracic diameter—except that three cases whose cardiac-thoracic ratio did not quite reach $\frac{1}{2}$ (cases Ra and m 27, M 24, and Rm 34) were also considered definitely pathological because the roentgenogram revealed specific characteristic changes in the cardiac outline. The electrocardiographic findings which were considered as definitely pathological were classified under the following five headings: (1) P-wave changes—where the P-wave exceeded 0.10 second in duration, (2) P-R changes—where the P-R interval exceeded 0.20 second in duration, (3) QRS changes—where the *base* of the R-wave exceeded 0.08 second in duration, (4) T-wave changes—including negativity of the T-wave in one or more significant leads (not including an isolated T_s), as well as characteristic alterations in the T-wave configuration, such as coving, (5) definite axis deviations (marked ventricular preponderances), evidences of markedly increased or decreased voltage (only when extracardiac interfering factors were eliminated).

A perusal of the appended tables 2-A and 2-B, in which the definitely pathological laboratory findings are italicized, will clarify the above criteria. In order to arrive at a quantitative estimate of the sum of laboratory evidences of disease it was decided to count each group of significant findings, as arranged under the headings outlined in the preceding paragraph, as constituting a unit of laboratory evidence of disease. So that, the maximal index of laboratory evidence for any individual case would be six units (one roentgen-ray and five electrocardiographic units all indicating definite pathological readings). The unit score for each case we may term the "laboratory pathology factor" (L.P.F.) for that case, thus, case A-12 which shows the following definitely pathological laboratory findings: P equals 0.12 second, PR equals 0.24 second, QRS equals 0.12 second, coronary type T-waves, poor electromotive force has an L.P.F. of 5, while Case Ra and m 22 which has a cardio-thoracic ratio of 0.5 and a marked right ventricular preponderance as the only definitely pathological laboratory findings has an L.P.F. of 2.

TABLE IIB
Organic Cardiac Cases *Not* Manifesting Tachypnea after Exercise

Case Key No	Post exercise Pulse/Respiratory Rate	Post exercise Pulse/Respiratory Ratio (P/R)	X-Ray Findings (Cm) (Cardiothoracic Ratio)	(In Seconds) Electrocardiograph Findings					Laboratory Pathology Factor (LPF) and Remarks
				Dura- tion "P"	Dura- tion "PR"	Changes of "QRS" (R Base Width)	"T" Wave Changes	Axis Deviation	
Rm 31	132-18	7.33	11.5/27	08	16	05	—	—	LPF-0
Rm 39	120-18	6.66	13.7/30.5	14	24	06	—	—	LPF-II
Rm 55	96-18	5.33	12/29.2	08	16	08	—	—	LPF-0
Rm 58	96-20	4.8	12.7/29	08	16	06	—	—	LPF-0
Rm 59	96-14	6.85*	None	09	18	04	—	—	LPF-0
Rm 61	126-20	6.3	13.7/29.5	12	20	06	—	Slight RAD	LPF-I
Rm 62	144-12	12	10.6/26.6	07	14	07	—	Slight RAD	LPF-0
Rm 63	126-18	7	12/26.7	10	24	08	—	—	LPF-I
Rm 64	102-22	4.64	12/27.2	08	16	08	—	—	LPF-0
Rm 67	126-18	7	13.1/30.5	08	17	07	T ₃ neg	LAD	LPF-I
Ra & m 23	96-15	6.4	13.8/28	08	17	06	—	Slight LAD	B P 196/125
Ra & m 26	144-20	Resting 7.2=7.2	14/29	12	24	08	T ₁ , T ₃ flat, T ₂ diphasic	—	LPF-0
Ra & m 27	132-20	6.6	14/29 full left border	12	20	12	T ₁ diphasic	RAD	LPF-III
Ra & m 32	126-12	10.5	16/30	09	18	08	T ₂ , T ₃ neg	LAD	LPF-IV
Ra & m 38	90-18	5	12.7/30.4	12	20	12	T ₁ 2 3 diphasic	Slurred	LPF-III
Ra 14	102-22	4.6*	13.2/27.5 <i>corvus</i> <i>arteriosus</i> 7.5	10	20	06	—	—	B P 160/110 LPF-III LPF-I

TABLE IIB—Continued

Case Key No	Post-exercise Pulse/Respiratory Rate	Post exercise Pulse/Respiratory Ratio (P/R)	X-Ray Findings (Cm) (Cardiothoracic Ratio)	(In Seconds) Electrocardiograph Findings					Laboratory Pathology Factor (LPF) and Remarks
				Dura- tion "p"	Dura- tion "PR"	Changes of "QRS" (R Base Width)	"T" Wave Changes	Axis Deviation	
M 14	126—18	Resting 9 > 7	12/29 5	20	24	08	—	RAD	LPF—III
M 15	120—20	6	None	08	15	08	—	Slight RAD	LPF—0 Female Case
M 23	90—18	5	13 8/28 4	08	18	05	T ₃ flat	—	LPF—0
M 24	90—15	6	12 8/27 <i>straight</i>	08	16	06	T ₃ neg	—	LPF—I
M 26	120—20	6	<i>left border</i>	10	20	04	—	RAD	LPF—I
H 40	102—14	7 3	12/29 5	08	16	10	—	—	LPF—I
H 39	96—18	5 33	13 8/31 2	08	16	06	—	—	B P 232/140
II 38	114—20	Resting 6 4 > 5 7	14 3/32	—	—	Slurred QRS 3	T ₁ neg	—	LPF—0
II 15	168—21	8	16 4/30 6	10	20	07	Diphasic T ₁	—	B P 190/130
L 6	108—15	7 2	11 8/28 5	08	16	07	—	Slight RAD	LPF—II
L 7	108—20	5 4	16/32	09	20	07	Diphasic T ₃	—	B P 210/100
A 8	126—12	10 5	11 7/25 5	12	20	06	—	—	LPF—0
A 9	96—18	5 33	13 8/28 5	12	20	06	—	—	B P 224/114
			15/28					Very high volt- age	LPF—I
									LPF—I
									LPF—III

Key to Table Same as for table 2A

Table 3 summarizes the scores which were arrived at in the indicated manner for the various clinical functional groups of cases. It shows that the group of organic cardiac cases as a whole showed an average L P F of 1.25. The group presenting an exercise tachypnea of 24 plus had an average

TABLE III
Complete Data Organic Cardiac Cases

Clinical Grouping	Total Number of Cases	Total Number of Laboratory Pathology Findings ("Unit")	Average Laboratory Pathology "Factor"	Number and Percentage of Cases with No Definite Pathological Laboratory Findings
With tachypnea (24 plus/ per minute) after exercise	27	40	40/27—1.48	6—22*%
Without tachypnea	29	30	30/29—1.03	12—41.4%
With "paradoxical" P/R ratio	15	21	21/15—1.4	3—20%
Without paradoxical P/R ratio	41	49	49/41—1.2	15—36.6%
With reduced pulse lability (P/R less than 4.5)	10	23	23/10—2.3	1—10%
Without reduced pulse lability (P/R greater than 4.5)	46	47	47/46—1.02	17—37-%
Total organic cases	56	70	70/56—1.25	18—32*%

L P F of 1.48, as compared with an average L P F of 1.03 for the group not showing tachypnea after exercise. In other words the group with tachypnea, on the average showed 44 per cent more definite laboratory evidence of disease than the group without tachypnea. Similarly, the group with a paradoxical pulse-respiratory ratio showed on the average, 16 $\frac{2}{3}$ per cent more definite laboratory evidence of disease than the group without a paradoxical pulse-respiratory ratio. Finally the group with a pathologically diminished pulse lability (pulse-respiratory ratio less than 4.5) showed on the average 125 per cent more laboratory evidence of disease than the corresponding group without a diminished pulse lability (pulse-respiratory ratio greater than 4.5).

The last column of table 3 indicates the reliability of using these clinical groupings in predicting the absence of laboratory findings of definite pathological significance. Thus the group without tachypnea showed an incidence of cases without pathologically significant laboratory findings that was 87 per cent greater than occurred in the group with tachypnea. Similarly the group without paradoxical pulse-respiratory ratio showed an incidence of "laboratory negative" cases 83 per cent higher than was found in the group exhibiting a paradoxical pulse-respiratory ratio. Finally in the group with-

out diminished pulse lability the incidence of "laboratory negative" cases was 270 per cent higher than in the group showing diminished pulse lability

Table 5 suggests another interesting clinical hint, which however would require statistical confirmation from a much larger series of cases, before it could be considered firmly grounded. In this graphic table, the average post-exercise pulse rates for organic cardiac cases with similar degrees of severity of laboratory pathology are plotted. The dotted line indicates these averages in the cases manifesting tachypnea of 24 plus, and the dash line indicates these averages in the cases manifesting no tachypnea. The graph suggests that in cases with tachypnea, a relatively slow pulse rate is more indicative of a severe lesion, while in the cases without tachypnea the reverse holds true,—viz, a relatively fast pulse rate is more indicative of a severe lesion. One is tempted to surmise that the reason for this is that with the more severe grades of functional cardiac impairment there generally co-exists a relative prolongation of the systolic phase of the cardiac cycle, so that the organism can more readily respond to the increased oxygenation demands of exercise by a relative greater utilization of the respiratory adjustment. However, insufficient data were at hand to adequately test this supposition.

TABLE IV

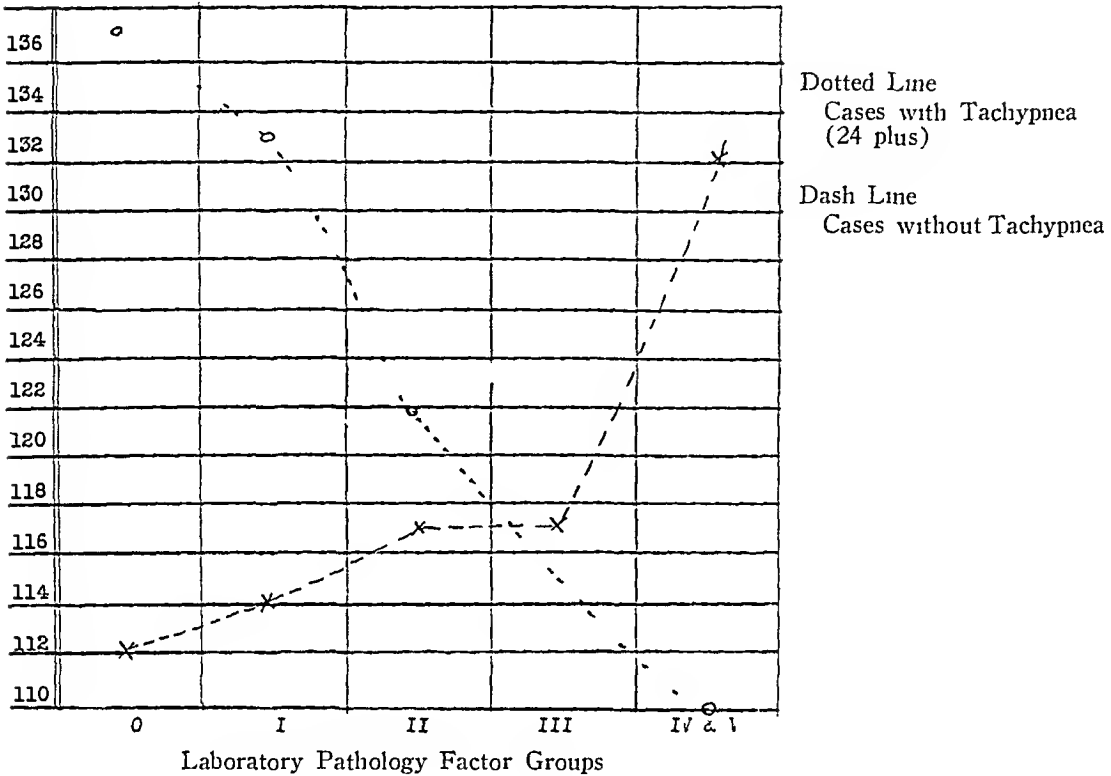
Comparison Roentgen-Ray Findings with Clinical Findings (Tachypnea) as to Sensitivity

Cases Showing	Number of Cases	Number of EKG—L P "Units"	Average L P Factor for EKG Findings—Alone	Number and Percentage of Cases with Negative EKG
1 Roentgen ray evidence of disease	12	13	1.08 plus	5—41 plus %
2 Tachypnea, 24 plus	27	35	1.3—	8—29.6 plus %
3 No tachypnea	29	23	.79 plus	15—51.6 plus %
4 Total organic cases	56	58	1.04—	23—41 plus %

Table 4 shows the relatively greater sensitivity of the simplest of these clinical criteria, viz, tachypnea, as compared with the commonly used laboratory criterion of pathological roentgen-ray findings. The electrocardiographic findings as expressed in laboratory factor averages are charted against these criteria. It seems clear that the presence of pathological roentgen-ray findings per se is no better indication of the presence of pathological EKG's than the diagnosis of organic heart disease per se. (Compare items (1) and (4) in the table.) On the other hand, the presence of tachypnea (after exercise) per se, affords a 20 per cent higher correlation with positive electrocardiographic findings, and a 25 per cent lower correlation with entirely negative electrocardiographic findings. (Compare items (1) and (2).)

TABLE V

Graph Indicating the Average Post-Exercise Pulse Rates for Groups of Cases with Identical Laboratory Pathology Factors (LPF)



SUMMARY

1 No entirely satisfactory clinical method has been available for the estimation of the degree of impairment of cardiac function in ambulatory organic cardiac cases

2 Laboratory findings per se (roentgen-ray and electrocardiographic data) afford certain reliable *objective* criteria for the estimation of impairment of cardiac function in such cases

3 This study of some 200 odd cardiac cases and 100 odd controls aims to determine the correlation existing between certain readily observable objective clinical data and the corresponding laboratory data. The tabular studies rather confirm the impression that a relatively high incidence of laboratory findings indicating functional impairment is found in those organic cardiac cases showing the following clinical signs

- (a) Tachypnea after exercise,
- (b) "Paradoxical pulse/respiratory ratio" after exercise,
- (c) "Diminished pulse lability" in response to exercise

The definition of these terms is made clear in the text

4 These studies were made on a clinical group of cases (mainly World War veterans) falling predominantly into certain age groups. Similar studies should be made on other more diverse age groups, before the conclusions arrived at can be considered generally firmly grounded.

5 The most tangible deduction from this study may be expressed in the following clinical aphorism. In an organic cardiac case manifesting tachypnea after exercise, a relatively slow pulse rate after exercise is more indicative of a severe lesion than a relatively fast one.

In closing it is pertinent to reemphasize that these deductions and conclusions are considered to apply only to ambulatory organic cardiac cases, free of the influence of any drug therapy. Also that all the figures quoted represent averages, and so represent the usual tendency but not the invariable pattern of reaction of certain clinical groups of cardiac cases. In other words the clinical symptoms discussed, when present, may be considered as symptom-complexes suggestive of, but by no means pathognomonic of, the presence of impaired cardiac function. And conversely, the absence of these clinical symptoms may be considered as suggestive evidence, but again by no means conclusive evidence, of the absence of a significant impairment of cardiac function.

The author wishes to express his indebtedness to Dr Reginald S. E. Murray of the Veterans' Facility, Lyons, N. J., as without his cooperation in furnishing extremely accurate and painstaking roentgen-ray and electrocardiographic reports, this study would have been impossible.

BLOOD VELOCITY RATE AND VENOUS PRESSURE IN THE PROGNOSIS OF HEART DISEASE¹

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THE heart is well adapted to study because of its anatomical position and the numerous expressions of its activity. It may be easily observed as to size, shape, the state of its valves and the character of muscular contraction. Its situation in the thoracic cage, surrounded as it is by air-containing viscera, makes radiographic examination possible. By expelling its contents into a closed vascular system, it builds up the arterial, capillary and venous blood pressures and succeeds in imparting motion to a column of blood, i e , velocity. The intermittent character of its contractions makes itself evident in a pulse wave and causes the propagation of minute electrical currents which may be registered graphically and interpreted. The accurate measurement of the various expressions of the physiologic activity of the heart enables us to assemble valuable information as to the state of the cardiovascular system.

Much has been written on blood velocity rate and venous pressure in heart disease. Most of the work has consisted of observations on patients during one short phase in their lives. It was therefore most natural that an attempt should be made to ascertain what changes took place in the hemodynamics of the circulatory system, when the disease process had an opportunity to regress or progress over a longer period of time. It was of particular interest to determine whether or not our studies could be of aid in prognosis.

Fifty-one cases of heart disease, rheumatic, arteriosclerotic and hypertensive, who were in-patients at the Jewish Hospital of Brooklyn, were studied. Forty-eight cases were traced one year later. Two were entirely lost. One was excluded because of the malignant nature of the disease. Of the 48, 17 were personally observed at the end of the test period. The remainder were followed through other institutions or through their family physicians.

The velocity rate (circulation time) was determined according to the method of Fishberg, Hitzig and King¹. Saccharin was injected intravenously in the antecubital fossa and the time which elapsed between the injection and the patient's experiencing a sweet taste was measured. The normal rate ranges from 9 to 16 seconds.

Venous pressure was measured by the direct method of Taylor, Thomas and Schleiter who employed an 'L'-shaped tube which was connected with a needle placed in a vein under standard conditions². The normal values are from 4 to 8 centimeters of blood.

* Received for publication October 8, 1936

From the Medical Service of Dr M A Rabinowitz, Jewish Hospital of Brooklyn, New York

TABLE I

Patient No	Diagnosis	C T	V P	(V P) ₂	One Year Later		
					C T	V P	(V P) ₂
1	Acute rheumatic fever, mitral regurgitation	<i>seconds</i> 10 0	7 5	—	*		
2	Acute exacerbation of rheumatic fever, mitral regurgitation and stenosis, pericardial effusion	10 0	10 5	10 5	18 0	5 0	5 0
3	Acute rheumatic fever, mitral regurgitation and stenosis, polyarthritis	10 0 11 0	9 5 8 0	9 5 8 0	*		
4	Acute exacerbation of rheumatic fever, mitral and aortic regurgitation and stenosis, polyarthritis	12 0 10 0	13 0 —	15 0 —	No Trace		
5	Acute exacerbation of rheumatic fever, mitral regurgitation and stenosis, pancarditis, aortic regurgitation, auricular fibrillation	16 0 13 5 12 0 17 0 17 0	8 5 7 5 11 5 4 0 8 0	— 9 5 — 7 0 9 0	Died		
6	Subacute bacterial endocarditis	15 0	10 0	10 0	Excluded (a)		—
7	Acute rheumatic polyarthritis, mitral stenosis	19 0 21 0	6 0 9 5	— 9 5	17 0	3 5	3 5
8	Subacute polyarthritis, mitral regurgitation and stenosis	15 0	8 0	8 0	*		
9	Acute exacerbation of rheumatic fever, pancarditis, pericardial effusion, rheumatic pneumonitis, mitral and aortic regurgitation and stenosis	15 0 12 5 11 0 16 0 10 0	7 5 7 5 11 0 7 5 6 5	10 0 — 15 0 8 5 6 5	17 5	5 5	5 5
10	Chronic rheumatic valvular disease, mitral regurgitation and stenosis, C P C of lungs, liver and extremities	15 0	6 0	16 0	*		
11	Chronic rheumatic valvular disease, mitral and aortic regurgitation and stenosis, auricular fibrillation, C P C of the lungs and liver	30 0	12 0	19 0	Died		

TABLE I—Continued

Patient No	Diagnosis	C T	V P	(V P) ₂	One Year Later		
					C T	V P	(V P) ₂
12	Chronic rheumatic valvular disease, mitral stenosis, auricular fibrillation, cardiac cirrhosis of the liver, ascites, umbilical hernia	<i>seconds</i> 20 0 10 0 15 0	12 0 13 5 14 0	16 0 13 5 22 0	*		
13	Chronic rheumatic valvular disease, mitral and aortic regurgitation and stenosis, auricular fibrillation, cardiac cirrhosis of the liver, C P C of lungs, liver and extremities	29 0	22 0	30 0	28 0	18 5	—
14	Chronic rheumatic heart disease, mitral regurgitation and stenosis, C P C of the lungs, coronary sclerosis, anginal syndrome	26 0 15 0	7 5 7 0	8 5 9 0	Died		
15	Chronic rheumatic heart disease, mitral regurgitation and stenosis, C P C of the lungs, liver, auricular fibrillation	17 0	9 5	9 5	*		
16	Chronic rheumatic heart disease, acute exacerbation, mitral regurgitation and stenosis, C P C of the lungs and liver, auricular fibrillation	21 0 15 0 23 0 22 0 17 0	21 5 12 5 18 0 15 0 —	15 5 20 0 20 0 —	*		
17	Chronic rheumatic heart disease, mitral regurgitation and stenosis, auricular fibrillation, embolization to extremities and mesenteric arteries	31 0	11 0	11 0	Died		
18	Chronic rheumatic heart disease, mitral regurgitation and stenosis, C P C of lungs, liver and extremities	25 0 35 0	7 5 —	9 0 —	Died		
19	Chronic rheumatic heart disease, mitral regurgitation and stenosis, C P C of the lungs, hyperthyroidism	12 0	8 5	10 5	13 5	3 5	3 5
20	Chronic rheumatic heart disease, (lues), mitral regurgitation and stenosis, aortic insufficiency, auricular fibrillation	19 0	9 5	8 5	*		
21	Chronic rheumatic heart disease, mitral regurgitation and stenosis, aortic regurgitation and stenosis, auricular fibrillation, decompensated	37 0 45 0	17 0 —	23 0 —	50 0 (b)	—	—

TABLE I—Continued

Patient No	Diagnosis	C T <i>seconds</i>	V P	(V P) ₂	One Year Later		
					C T	V P	(V P) ₂
22	Chronic rheumatic heart disease, mitral and aortic regurgitation and stenosis, auricular fibrillation, decompensated, hyperthyroidism	55 0 45 0	17 0 15 0	23 0 23 5	* (c)		
23	Congenital heart disease, interventricular septum defect, decompensated	17 0	15 0	18 0	12 0	11 0	15 0
24	<i>Arteriosclerotic Heart Disease</i> Coronary sclerosis, myofibrosis cordis, anginal syndrome	14 0 16 0	— 7 0	— 7 0	*		
25	Coronary sclerosis, anginal syndrome	12 0	9 5	10 50	*		
26	Coronary sclerosis, acute coronary artery thrombosis	17 0	8 5	9 5	20 0	2 5	3 0
27	Acute coronary artery thrombosis, generalized arteriosclerosis, diabetes mellitus	13 5 17 0	5 5 7 0	— 7 0	*		
28	Coronary sclerosis, generalized arteriosclerosis, anginal syndrome	20 0	18 0	18 0	18 0	4 0	6 0
29	Coronary sclerosis, myofibrosis cordis, anginal syndrome, diabetes mellitus	25 0 22 0	6 0 9 5	8 0 10 0	*		
30	Coronary sclerosis, acute coronary thrombosis, ventricular aneurysm	20 0 22 0	3 0 7 0	4 0 10 0	15 0	7 5	7 5
31	Coronary sclerosis, anginal syndrome	19 5	15 5	—	15 0	8 0	8 5
32	Acute coronary artery occlusion	21 0	6 5	6 5	Died		
33	Coronary sclerosis, diabetes mellitus, cystopyelitis	17 0	12 0	12 0	*		
34	Acute coronary artery occlusion, coronary sclerosis, myofibrosis cordis, ventricular aneurysm, ventricular fibrillation	20 0	—	—	Died		
35	Coronary sclerosis, myofibrosis cordis, congestive failure	31 0 — 39 0	25 0 20 0 10 0	— — —	* (d)		

TABLE I—Continued

Patient No	Diagnosis	C T	V P	(V P) ₂	One Year Later		
					C T	V P	(V P) ₂
36	Coronary sclerosis, congestive heart failure, anginal syndrome	<i>seconds</i> 45 0 46 0	14 0	21 0	Died		
37	Coronary sclerosis, complete heart block, Stokes-Adamssyndrome, decompensated	25 0 28 0	16 5 —	— —	*		
38	Coronary sclerosis, generalized arteriosclerosis, myofibrosis cordis, decompensated with anasarca	17 0 17 0 20 0	16 5 6 5 —	30 0 7 5 —			
39	Coronary sclerosis, myofibrosis cordis, congestive heart failure, splenomegaly	34 0 43 0 — 45 0	13 5 16 0 17 5 12 0	17 5 21 0 18 5 12 0	Died	1 0	1 0
40	Acute coronary artery occlusion, coronary sclerosis, congestive heart failure	35 0	12 0	17 0	Died		
41	Coronary artery disease, myofibrosis cordis, anginal syndrome	31 0	9 0	—	Died		
	<i>Hypertensive Heart Disease</i>						
42	Hypertension, confluent bronchopneumonia, thrombosis of the leg, pulmonary infarct	15 0	10 0	10 0	12 0	9 5	9 5
43	Hypertension, generalized arteriosclerosis, cardiac hypertrophy and dilatation, decompensated	38 0	21 0	30 0	* (e)		
44	Hypertension, generalized arteriosclerosis, coronary sclerosis, lues, toxic thyroid adenoma	14 0	3 0	3 0	14 6	5 5	8 5
45	Essential hypertension, coronary sclerosis, auricular fibrillation, congestive heart failure, chronic cholecystitis	23 0 30 0	9 5 8 5	12 0 13 0	13 0 (f)	4 0	11 0
46	Hypertension, generalized arteriosclerosis, cardiac hypertrophy and dilatation, decompensated, chronic nephritis, cerebral hemorrhage	—	26 0	30 0	Died		
47	Essential hypertension, nephrosclerosis, asthmatic bronchitis	14 0	8 0	—	30 0	21 0	28 0

TABLE I—Continued

Patient No	Diagnosis	C T	V P	(V P) ₂	One Year Later		
					C T	V P	(V P) ₂
48	Hypertension and arteriosclerosis, coronary sclerosis, hypertensive retinopathy, chronic uremia	<i>seconds</i> 15 0	7 0	7 0	No Trace		
49	Hypertension and arteriosclerosis, coronary sclerosis, myofibrosis cordis, myocardial failure, auricular fibrillation	27 0 51 0 24 0	6 0 9 5 4 0	— 13 5 4 0	Died		
50	Hypertension and arteriosclerosis, coronary sclerosis, decompensated, auricular flutter	42 0 34 0 35 0 20 0 20 0	30 0 21 5 14 0 14 5 15 0	30 0 30 0 — 21 0 16 0	(g)		
51	Hypertension and arteriosclerosis, coronary sclerosis, decompensated, diabetes mellitus	17 0	7 5	8 5	*	28 0	30 0

C T—Circulation time in seconds

V P—Venous pressure

(V P)₂—Venous pressure after pressure over right upper quadrant

* Patient living, traced through family physician or hospital

(a) not included in statistical survey because of malignant nature of the disease

(b), (c), (d), (e), (g), Velocity rate at first observation 30 seconds At the end of one year functional capacity Class 3 Patient No 50

died 20 months after first observation Patient No 21 died immediately post-thyroidectomy

(f) Velocity rate at first observation 30 seconds At the end of one year functional capacity Class 2a

In arranging the tables which follow, in those cases on which more than one observation was made, the slowest velocity rate and the greatest venous pressure (not necessarily the coincidental one) were chosen. This was done because it was felt that these figures represented the greatest inefficiency which was registered by the particular circulatory system under study.

TABLE II

Circulation Time	Number of Cases	Number of Deaths in One Year	Mortality %
9-16 seconds	13	0	0
17-29 seconds	21	4	19%
30 seconds or more	14	8	57%

Case 50 is included in the preceding table, but it is not noted as a death. A total ablation of the thyroid gland was done 10 months after a circulation time of 42 seconds was recorded. The patient lived for another 10 months. Case 21 is also included in the above tables and is not listed as a death because death followed immediately after thyroidectomy. The operative procedure was done one year after the patient was first observed and was decided upon only after his decompensation failed to respond to any form of therapy. Cases 6 and 46 were excluded entirely. The first was one of subacute bacterial endocarditis, the second patient was semicomatose and the circulation time could not be obtained.

Berinskaya and Meerzon concluded that a marked slowing of the blood velocity had a bad prognostic significance.³ Fishberg, Hitzig and King presented a study of 59 cases of recent myocardial infarction in the *Archives of Internal Medicine* of December 1934.⁴ In 38 of these the circulation time was recorded. The following is adapted from table 3 of their article.

TABLE III

Circulation Time	Number of Cases	Number of Deaths	Mortality %
9-16½ seconds	9	1	11%
17-29½ seconds	15	2	13%
30	14	9	64%

(Adapted from Table 3 of article by Fishberg, Hitzig, and King⁴)

In both tables 2 and 3, it is evident that the mortality rate increases rapidly when the circulation time exceeds 30 seconds. The cases of Fishberg et al. were all of recent myocardial infarction and apparently were not followed up after the original investigation. It is probable that with a 12 month follow-up their markedly delayed velocity group would have presented much higher mortality rates.

In our mixed series, at the end of one year, there were six patients whose velocity rates exceeded 30 seconds and who were still alive. The importance of the finding of a very slow velocity rate is emphasized by the fact that of these six patients, five belonged to Class 3 and became decompensated on the slightest exertion. The sixth showed a remarkable improvement. At the end of the year his circulation time fell from 30 to 13 seconds. The following are synopses of the histories of these cases.

CASE REPORTS

(No 22) R F, male, aged 45 years. Chronic rheumatic valvular heart disease, mitral regurgitation and stenosis, auricular fibrillation, congestive heart failure. On admission, there were dyspnea, cyanosis, râles at both bases, fluid in the pleural and abdominal cavities and a liver enlarged to the iliac crest. The circulation time was 55 seconds. The venous pressure was 17 centimeters, and it rose to 23 centimeters after right upper quadrant pressure. Since then, he has had repeated episodes of decompensation and is incapable of even the slightest exertion. Class 3.

(No 43) I L, female, aged 45 years. Hypertension, arteriosclerosis, cardiac hypertrophy and dilatation, decompensation. On examination, the patient was dyspneic, cyanotic and had sacral and pretibial edema. The heart was enlarged both to the right and left. There was an apical systolic murmur. The liver was enlarged to 8 centimeters' breadth below the costal edge. There was ascites. The eye-grounds showed arteriosclerotic blood vessel changes. The blood pressure was 230 mm of mercury systolic and 124 diastolic. The circulation time was 38 seconds, the venous pressure was 21 centimeters. The patient decompensates very quickly* and with little exertion. Class 3.

(No 50) H B, male, aged 53 years. Hypertension, generalized arteriosclerosis, coronary sclerosis, myofibrosis cordis, auricular flutter, congestive failure with enlarged liver, pulmonary stasis and peripheral edema. The blood pressure was 240 systolic and 120 diastolic. The circulation time was 42 seconds. The venous pressure was greater than 30 centimeters. The patient was readmitted twice within a period of nine months. The last circulation time was 27 seconds. On the third admission (10 months after the first observation) an ablation of the thyroid gland was done. It was most interesting to observe that, immediately following thyroidectomy, the heart rate changed from an auricular flutter to a regular sinus rhythm. Upon discharge the patient was still slightly decompensated. The circulation time was 27 seconds. The venous pressure was 19 centimeters. He was then admitted to an institution for chronic diseases. There he had several attacks of precordial pain and pulmonary edema. He made a sudden exitus 20 months after the first circulation time of 42 seconds was recorded. Class 3.

(No 35) E C, female, aged 55 years. Generalized arteriosclerosis, coronary sclerosis, myofibrosis cordis, anginal syndrome of nine years' duration, congestive heart failure with râles at both bases, a liver enlarged to 8 centimeters' breadth below the costal edge, and ankle edema. On admission the circulation time was 31 seconds. The venous pressure was 25 centimeters. Her family physician reported one year later that she was confined to bed for more than two-thirds of the time and that she decompensated with mild exertion. Class 3.

(No 21) P W, male, aged 44 years. Chronic rheumatic heart disease, mitral regurgitation and stenosis, aortic regurgitation and stenosis, auricular fibrillation, decompensated. On examination, there were orthopnea, cyanosis, fine crepitant râles at both bases and also large sonorous râles throughout the chest. The heart was enlarged to the right and left and the liver edge was felt at the level of the umbilicus.

On two separate occasions the circulation time was 37 seconds and 45 seconds. The venous pressure was 17 centimeters. After a month, he was discharged as improved. He was followed in the out-patient department where he always showed some evidence of decompensation. Eleven months after his first admission he returned to the hospital markedly decompensated. The circulation time was 50 seconds. There was a slight improvement after therapy and then a remission. A total ablation of the thyroid gland was decided upon. Unfortunately, the patient succumbed to the procedure. Class 3.

(No 45) S W, female, aged 48 years. Hypertension, generalized arteriosclerosis, coronary sclerosis, auricular fibrillation, anginal syndrome, congestive failure with enlarged liver. The circulation time was 30 seconds. The venous pressure was 9.5 centimeters and it rose to 12 centimeters after pressure was made over the liver area. In the year that followed she enjoyed fairly good health except for occasional precordial distress. When we observed this patient a year later there was no dyspnea or cyanosis. The lungs were clear. The apex beat was in the sixth interspace two inches outside the mid-clavicular line. She was fibrillating. Blood pressure was 190 systolic and 120 diastolic. The circulation time was 13 seconds. The venous pressure was 6 centimeters and rose to 13 centimeters after making abdominal pressure. Class 2A.

TABLE IV

Venous Pressure	Number of Cases	Number of Deaths in One Year	Mortality %
0- 8 centimeters	16	3	18.7%
9-19 centimeters	26	8	30.7%
20 centimeters or more	6	1	16.6%

It is evident that there is not the same progressive correlation between increasing mortality rate and increasing venous pressure that there is between mortality rate and increasing circulation time.

We were able to recall 17 patients at the end of one year. A complete physical examination and a determination of the circulation time and the venous pressure were done. The results are tabulated in columns 6, 7, 8, of table 1. Cases 2, 9, 47, 21, 45, and 50 were of unusual interest. The last three have already been discussed.

CASE REPORTS

(No 2) D S, female, aged 21 years. Acute exacerbation rheumatic fever, mitral regurgitation and stenosis, pericardial effusion. She suffered her first attack of rheumatic fever 14 years before her present admission. On examination she showed marked pallor, dyspnea, slight cyanosis and fever. There was dullness at both bases. The heart outline by percussion showed enlargement both to the right and left. The heart tones were muffled. There were presystolic and systolic apical murmurs and a pericardial friction rub. There was no peripheral edema and no enlargement of the liver or spleen. The circulation time was 10 seconds. The venous pressure was 10.5 centimeters. She made good progress and was discharged much improved.

One year later, she returned for an examination. She reported that she felt well on ordinary effort, but that she was no longer able to indulge in tennis or swimming without dyspnea whereas before her last illness she had experienced no difficulty in

these sports. Our physical examination showed no evidence of congestive failure. The heart was slightly enlarged to the left. There was an apical systolic murmur and an accentuated pulmonic second sound. Her circulation time was now 18 seconds, a marked increase over that of the preceding year. The venous pressure was 5 centimeters.

(No 47) E. D., female, aged 44 years. Essential hypertension, nephrosclerosis, congestive heart failure. Her chief complaint was repeated attacks of whistling in the chest with shortness of breath. She appeared chronically ill. There were many musical wheezing râles, with the prolonged expiration, throughout the chest. There was an accentuated aortic second sound. The liver edge was palpable. There was no peripheral edema. She was tested in another clinic and found to be sensitive to feathers. There was much discussion as to whether the asthmatic attacks were allergic or due to heart failure. The circulation time was 14 seconds. The venous pressure was 8 centimeters. This, certainly, did not point toward the heart as being the seat of disease and responsible for the symptoms. In relation to this, we must call attention to the report of Winternitz on two cases of so-called "cardiac asthma" where the circulation time was normal.¹⁰

One year later she reported that after leaving the hospital she had been ill in bed for two months. She now showed a blood pressure of 220 systolic and 140 diastolic and a pulse rate of 96. The heart was enlarged to the right and left. There was an apical systolic murmur and an accentuated second aortic sound. There were no râles in the chest. The liver was palpated 4 centimeters below the costal edge. There was marked ankle edema. The circulation time was 30 seconds. The venous pressure was 21 centimeters and after right upper abdominal pressure it rose to 28 centimeters. There was no question now that there was myocardial insufficiency both from the physical examination and the determinations of the velocity rate of the blood and of the venous pressure.

(No 9) S. L., male, aged 19 years. Acute exacerbation of rheumatic fever, pancarditis, pericardial effusion, rheumatic pneumonitis, mitral and aortic regurgitation and stenosis. On admission he showed dyspnea and cyanosis. There was dullness at both bases and evidence of a pericardial effusion. The liver was slightly enlarged. There was no peripheral edema. The problem which presented itself was whether or not this patient was suffering from myocardial failure with decompensation or whether the underlying process was purely a severe rheumatic infection. It was the prevailing opinion that we were dealing with an acute exacerbation of an old rheumatic heart disease. This was borne out by the therapeutic test when the patient failed to respond to digitalization and diuretics. Fever continued for weeks and subsided with the return of the physical findings to a more normal state. The circulation time varied from 14 to 16 seconds. The venous pressure averaged 7.5 to 11.0 cm. He showed marked improvement.

One year later he returned saying that he had been well and had been working as a salesman with no distress. Our findings at this time were that he had no dyspnea or cyanosis and no peripheral edema. There were no râles in the chest. The apex beat was found in the sixth interspace one inch outside of the mid-clavicular line. The circulation time was 17.5 seconds. The venous pressure was 5.5 centimeters.

DISCUSSION

There appear in the literature two main theories as to the mechanism of heart failure. The first and oldest is the "back-pressure" hypothesis which stressed the concept that failure of any chamber resulted in a damming up of blood behind that chamber.⁵ Thus, dyspnea on effort and pulmonary

edema were ascribed to failure of the left ventricle which resulted in pulmonary congestion. Cardiac insufficiency associated with passive congestion of the liver and peripheral edema was attributed to failure of the right ventricle. The second and later assumption placed emphasis on diminished cardiac output as the principal factor.⁶ Proponents of this belief explained pulmonary edema as being due to a failure of the right ventricle while the responsibility for increased venous pressure with peripheral edema fell upon a failing left ventricle which was incompetent in propelling sufficient blood.

In his treatise on the failure of the circulation, Harrison says, "the theory of diminished cardiac output must be discarded, for this hypothesis fails to account for the symptoms, and measurements of the cardiac output have shown that heart failure may be associated with a normal output of the heart and that clinical improvement may be accompanied by a change in either direction or by no change of this function. The back pressure theory on the other hand offers an acceptable explanation of dyspnea and edema formation, is compatible with the clinical and pathological findings, and is in accord with the 'law of the heart' and other fundamental physiological principles."⁷

The French school of medicine has been noted for adherence to the back pressure theory and for insistence on the distinction between left heart and right heart failure. To Coisvart, Beau and Potain, the only picture of heart failure was that which we know of as right heart insufficiency. Fraentzel, Meiklen, Vaquez, Frank and Lian recognized failure of the left ventricle as a distinct entity.⁸

Left ventricular failure is brought about by hypertension, aortic valvular disease and myocardial infarction involving particularly the left ventricle. The most prominent symptoms are dyspnea and substernal oppression on exertion, paroxysmal dyspnea and acute pulmonary edema. The underlying pathology is venous stasis affecting the pulmonary circuit.⁸

Pure right heart failure with congestion of the liver and peripheral edema is most commonly seen in association with chronic pulmonary disease, congenital heart affections, tricuspid lesions and lesions affecting the pulmonary artery.

Right heart failure may be engrafted upon a chronic failing left heart. Thus, right and left heart failure may and frequently do, coexist.

Mitral stenosis is peculiar in that it places a mechanical obstruction in the out-flow tract of the lesser circulation. Pulmonary congestion, therefore, in this instance, is not predicated upon the basis of left heart failure.

There is an interesting syndrome of heart failure first described by Bernheim at Nancy in 1910.⁹ He observed a group of cases of congestive heart failure with (a) enlargement of the liver, (b) peripheral edema, (c) absence of râles in the lungs, (d) enlargement of the left ventricle. At autopsy he noted that the hypertrophy of the left ventricle was associated with a marked hypertrophy of the interventricular septum which encroached

upon the lumen of the right ventricle so that there existed virtually a functional stenosis of that chamber. The symptomatology and the physical findings can be explained only by back pressure due to stasis behind the right ventricle. It is possible, therefore, for right heart failure to precede left heart failure even though the underlying disease process is in the left ventricle.

Congestive heart failure with hepatomegaly and peripheral edema is always accompanied by an increase in venous pressure. We may therefore utilize the measurement of venous pressure as a criterion of the degree of right heart failure. A necessary corollary, therefore, is that the absence of increased venous pressure rules out right heart failure.

In cardiac failure there is a slowing of the speed of blood flow (velocity). Thus, if the circulation time (rate of blood flow) is measured and found to be slower than normal, and if, at the same time, the venous pressure is measured and found to be within normal limits, it may be concluded with reason that there exists an inefficiency of the left ventricle. There is, then, in the simultaneous determination of the circulation time and venous pressure, a method of distinguishing right from left heart failure.

We have found that there is no necessary parallel between the venous pressure (criterion of congestive heart failure) and the slowing of the blood velocity. In table 1, patients 12, 14, 35 and 39 show that in the same patient at different times in his clinical course, the rate of blood flow and the venous pressure varied markedly without showing any direct relationship to each other. In other patients we have observed very slow velocity rates with absolutely no sign of congestive failure as in patients 17, 29, and 41. Fishberg et al have demonstrated that there may be a normal or subnormal venous pressure in isolated failure of the left ventricle although there is a marked slowing of the circulation time.

It is obvious then, since the mortality rate varies directly with the circulation time and not with the venous pressure (venous pressure = index of right heart failure), that the mortality rate is dependent upon the efficiency of the left ventricle. Hence, left ventricular failure is of graver import than right ventricular failure.

Increased venous pressure can be detected without difficulty by simple physical examination. However, the circulation time can be determined only by some special procedure of which, fortunately, there are several simple ones.^{1, 11}

Since the mortality rate varies rather regularly with the blood velocity, it is clearly evident in the determination of the circulation time, there exists a real adjunct in the prognosis of heart disease.

The determination of the blood velocity has also been found useful

- (1) In differentiating dyspnea due to myocardial failure from that of bronchial asthma, cerebral and pulmonary dyspnea.¹⁰
- (2) In determining whether or not an anginal syndrome is associated with the presence of myocardial damage.¹⁰

- (3) In separating ascites and edema of cardiac from that of extra-cardiac origin¹⁰
- (4) In uncovering a masked hyperthyroidism in the face of heart failure^{10, 11, 12}

In passing we must mention that Fishberg and his co-workers have practised making pressure on the liver while obtaining the venous pressure. This was done routinely in all of our cases. We too, have found that making pressure over the right upper quadrant of the abdomen while the manometer is in the antecubital vein is of aid in determining whether or not a hepatomegaly is due to venous engorgement. In 19 cases, where there was no congestive heart failure, the average rise in venous pressure on squeezing the liver area was 0.5 centimeters. In 23 cases, where congestive heart failure with an enlarged liver was present, the average rise was 5.6 centimeters, and varied from 2 to more than 14 centimeters.

CONCLUSION

In a series of 51 cases of rheumatic, arteriosclerotic and hypertensive heart disease, 48 of which were traced for at least one year, we have found that

- 1 The circulation time is of greater significance in prognosis than the venous pressure

- 2 The mortality rate increases as the velocity of the blood flow decreases and that when the circulation time is 30 seconds or more, the mortality rate is 57 per cent for one year

- 3 Of the six patients with a circulation time greater than 30 seconds and alive at the end of a year, five were in Class 3 and decompensated with the slightest effort. The sixth patient improved clinically and the velocity rate fell from 30 to 13 seconds

- 4 Failure of the left ventricle is of graver import than failure of the right ventricle

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THE COMPLICATIONS AND HAZARDS OF FEVER THERAPY ANALYSIS OF 1000 CONSECUTIVE FEVER TREATMENTS WITH THE KET- TERING HYPERTHERM *

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THE beneficial effect of intercurrent infection upon patients with chronic disease was noted many years ago and naturally suggested the therapeutic value of elevated body temperatures. The feasibility of such a form of non-specific treatment was tested with tuberculin shortly after its introduction about 50 years ago. This was the first of a long series of suggestions for therapeutic fever production which have included the utilization of febrile diseases, protein fevers and numerous mechanical and electrical devices. Despite the large number of methods which have been recommended and are available, the end is not yet in sight, and scarcely a month passes without the proposal of a new device or a further refinement of an old method. This interest and activity is encouraging, for all of the available methods seem to have disadvantages, and the completely ideal procedure for therapeutic fever production still remains to be developed.

From the standpoint of therapeutic results the least common denominator of all methods seems to be the type of fever which is produced. Sweeping aside all arguments as to technic, the method of choice depends upon the ease and certainty with which a desired level of fever can be reached and maintained, the expense involved, the familiarity of the operator with the method, and, most important of all, the safety and comfort of the patient.

Because certain complications and hazards encountered in fever therapy depend entirely upon the height and duration of fever regardless of the method of production, we feel justified in presenting our observations of 1000 consecutive fever treatments given with the Kettering Hypertherm at City Hospital, Cleveland, Ohio from March 1934 to January 1936. The therapeutic results will not be discussed at this time.

The influence of higher fevers and longer treatments in increasing the hazards to the patient can be demonstrated because the treatments comprising this series fall into two distinct groups. The largest group consists of 830 treatments, during which fever of 103° F to 105° F was maintained for periods of 3 to 5 hours. These treatments were given to patients with acute and chronic arthritis, syphilis and various other diseases. The second group consists of 170 treatments, during which fevers of 106° F to 107° F were maintained for periods of 4 to 7 hours in patients with gonorrhea and its

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complications For the sake of convenience, fevers of 103°F to 105°F will be referred to as mild treatments, and fevers of 106°F to 107°F will be referred to as severe treatments throughout the remainder of this paper

No attempt is made to compare the complications and hazards observed in this series with those reported by other workers We believe that most of the phenomena described here may be seen in any series of induced fevers of comparable elevations and duration except those, such as skin burns, which occur only when external heat is applied to the patient Complications such as severe debility due to an induced disease like malaria, or the increasing difficulty in producing successive fevers, as in protein therapy, are lacking in this series

Some comprehension of the method used is necessary for an understanding of the problems encountered in this series The apparatus consists of a cabinet large enough to accommodate comfortably the body of a man in a prone position with his head outside The cabinet is provided with a large sliding door on each side to allow for the taking of rectal temperatures, the periodic examination of the patient's skin and the arranging of blankets as necessary Fever is produced by passing heated and humidified air over the patient's body A separate compartment at the foot of the cabinet contains an electrical resistance coil heating element which heats the air, and a blower which causes it to circulate through the cabinet A second heating element produces humidity by boiling water Automatic controls maintain air temperature and humidity at the desired levels

The patient arrives at the treatment room about 8 o'clock in the morning after a light breakfast or in a fasting state After recording the temperature, pulse, blood pressure and weight, the patient is placed in the cabinet and all covering is removed The air temperature of the cabinet, which is about 125°F at the start of the treatment, is raised as rapidly as possible to 150°F or 160°F and the humidity is kept between 30 and 40 per cent This preliminary period, during which the patient's temperature becomes elevated to the desired level, varies from one-half to two hours, but this time is not included in recording the duration of the treatment When the desired degree of fever is attained, the body is covered with a light blanket, an electric fan is directed on the face, iced water or 0.6 per cent saline is given as desired and ice is rubbed on the face At this time the temperature and humidity of the air in the cabinet are adjusted to the lowest level at which the desired body temperature can be maintained When the treatment is finished the patient is removed from the cabinet, and the temperature falls in an hour or so to the pre-treatment level After a bath the patient is sent to the ward or allowed to go home

This study deals with 1000 consecutive fever treatments divided as mentioned above, into 830 mild treatments and 170 severe treatments The mild treatments were given to 142 patients of whom 62 had chronic arthritis, 21 had acute arthritis, 9 had rheumatic fever or chorea, 15 had syphilis and

35 had a variety of conditions. The patients with chronic arthritis had treatments at 103° F. to 104° F. for three to four hours, the others usually had 105° F. for five hours. The number of treatments per patient averaged 5.8, but varied from one treatment in 28 patients to 23 treatments in one patient. The severe treatments were given to 62 patients with gonorrhea, either genital or metastatic. An attempt was made to treat these patients at as near 107° F. as seemed consistent with safety, and this temperature was maintained in each treatment at least five hours, and preferably seven hours. Many of the patients in the first group who received mild treatments were debilitated, undernourished and aged beyond their years, while those in the second group who received severe treatments were young, robust and in excellent general health. Despite the marked difference in physical condition of the two groups, only 39, or 4.7 per cent, of the mild treatments had to be discontinued, compared to 24, or 14.1 per cent, of the severe treatments. Of the 39 mild treatments which were discontinued, 21 were discontinued because of insistence on the part of the patient, lack of cooperation or delirium, five because of blisters or burns, eight because of diarrhea or persistent vomiting, three because of shock and two because of tetany. Of the 24 severe treatments, 12 were discontinued because of insistence on the part of the patient, lack of cooperation or delirium, seven because of blisters or burns, two because of diarrhea or intestinal cramps and three because of shock. When these figures are arranged in parallel columns and reduced to percentages of treatments given, the difference between mild and severe treatments becomes apparent.

Our plan to weigh patients routinely before treatment and again prior to their discharge from the department was seriously disrupted because of the difficulty of getting them upon the scales. This was the case in arthritics with painful or disabling disease and in all patients with severe nausea or debility following treatment. The observed changes in weight during therapy were closely related to the amount of fluid ingested and to vomiting. We have data on 172 mild treatments. In 67 instances the weight after treatment was within one pound of the pre-treatment level. This was considered no change. In 19 instances there was a gain in weight which varied from one to six pounds, while in 86 instances there was a loss. In nine treatments the loss was less than three pounds, in 29 treatments it was three to five pounds and in 27 treatments it was five to seven pounds. In 21 treatments weight loss varied from seven to 15 pounds. Of these 21 treatments, 19 were given to three patients. Excessive weight loss occurred repeatedly in successive treatments of the same patients who took fluids poorly and vomited repeatedly. In 18 severe treatments, weight was unchanged in eight, there was a gain in five and a loss in five, never more than 6 pounds. The weight changes observed in fever treatments are temporary as restoration to pre-treatment weight takes place within 48 hours in most instances.

Nausea or vomiting is a frequent source of discomfort. Patients often

feel nauseated or vomit once or twice during the treatment but this occurs most often in the rest period following the treatment, particularly in patients who must get up and dress to go home. In rare instances, vomiting occurs with sufficient severity during the course of the treatment to necessitate its premature termination. Nausea or vomiting was observed in 28.1 per cent of the 830 mild treatments or 233 times, and in 35.5 per cent of the 170 severe treatments or 57 times. The patients who received repeated treatments were studied to determine if the incidence of nausea or vomiting increased with successive treatments and whether or not there was an individual susceptibility to nausea or vomiting. Of 114 patients who received two or more mild treatments, 45 had nausea or vomiting. These patients received 399 treatments, and nausea or vomiting occurred in 52 per cent or 207 times. Of 37 patients who received two or more severe treatments, 10 had nausea or vomiting. These patients received 67 treatments, and nausea or vomiting occurred in 55 per cent or 37 times. Thus it is seen that the vomiting patients receiving several treatments had this symptom in 52 per cent and 55 per cent of their treatments compared to 28.1 per cent and 33.5 per cent of the whole group. Some patients escape nausea entirely, even on repeated treatments, while patients with nausea receiving several treatments have a higher treatment incidence than the whole group.

It was thought that the use of morphine increased the incidence of these gastric disturbances, but the figures do not substantiate this view. In 830 mild treatments, morphine was administered 672 times or in 80.9 per cent of the treatments. Of the 399 treatments given to 45 patients who developed nausea, morphine was administered 307 times or in 77 per cent. In the 170 severe treatments, morphine was administered 145 times or in 85.3 per cent. Of the 67 severe treatments given to 10 patients who developed nausea, morphine was administered 52 times or in 74.6 per cent. When possible morphine was withheld on succeeding treatments of those patients who were nauseated or had vomited previously. Although these figures seem to indicate that morphine played little or no part in the causation of vomiting several individual patients escaped vomiting when morphine was omitted.

The effect of fever therapy in causing anorexia was observed by noting the first regular meal which the patient was able to eat after treatment. In 188 mild treatments the patient was able to eat supper on the day of treatment in 35 instances or in 18.6 per cent (no anorexia). He was able to eat breakfast the next morning in 123 instances or 65.4 per cent (anorexia for 12 to 18 hours), and he was unable to eat until the following noon in 30 instances or 16 per cent (anorexia for 18 to 24 hours). Of 56 severe treatments the patient ate his supper on the day of treatment in 20 instances or 35.7 per cent (no anorexia), breakfast next day was the first meal in 25 instances or 44.6 per cent (anorexia for 12 to 18 hours), and he was unable to eat until the following noon in 11 instances or 19.7 per cent (anorexia for 18 to 24 hours). This disparity between the two groups is remarkable, espe-

cially when one considers that the severe treatments were not terminated until later in the day, usually from three to five hours nearer supper time, than were the mild treatments. This is a further indication of the vigor and robustness of the patients treated for gonorrhea and the weakness and debility of the other group. Inasmuch as patients miss breakfast and lunch on the day of treatment prolonged anorexia is undesirable, especially in debilitated patients.

Burns which necessitate terminating fever treatments constitute but a small proportion of the burns produced. In most instances the burns are blisters of small size and heal without scar formation, although second degree burns have been seen. Patients are warned of this danger of burns and even of scars, particularly when severe treatments are contemplated, and therapy is not discontinued because of this unless it seems likely that burns will be severe. They occur only on the ventral surface of the body and are most frequently seen over bony prominences, in scars, on pendulous breasts or on those other portions of the skin which Bierman has shown to be relatively intolerant of heat. In 830 mild treatments, burns were observed in 18 instances or 2.2 per cent. In 170 severe treatments, however, burns were seen in 23 instances or 13.5 per cent. It must be remembered that these thermal injuries to the skin result from hot and humid air alone, for the fever cabinet is so constructed that the patient's skin cannot come in contact with a heating element.

Tetany was occasionally seen, but only two treatments were interrupted because of it. Many mild instances probably occurred for patients occasionally complained of muscle cramps or stiffness of the hands. This is usually seen early in the treatment as the body temperature is rising and before morphine is given. The symptoms are fleeting, usually promptly relieved by lowering the cabinet temperature temporarily, the administration of morphine or of calcium gluconate intravenously. The tetany which occurs during fever treatments is due to alkalosis caused by the hyperventilation resulting from the respiratory stimulus of hot air to the skin. No alteration in calcium metabolism occurs, and because tetany develops early in the treatment, it is probably not related to chlorine metabolism. Morphine, because of its effect in depressing respiration, seems the ideal preventative. We have not noted undue cyanosis from its use.

Herpes labialis occurred in 45 of the 142 patients given mild treatments, or 31.7 per cent, and in 19 of the 62 patients given severe treatments or 30.6 per cent. The figures are given in relation to the number of patients, rather than the number of treatments, because this complication occurs but once in an individual patient during any continuous series of treatments. On one or two occasions herpes labialis followed the second treatment only, but otherwise they were seen only after the first treatment. A second attack has been observed once in a patient whose last previous treatment was given more than three months earlier. Herpes labialis appears three to five days

after the first treatment, remains five days and heals without leaving a scar. The lesions may be very extensive, covering the lower half of the face including the external and internal nares and involving the buccal mucosa.

The rarest accident in our experience, but by far the most alarming, and the one which constitutes the greatest hazard in fever therapy, is the occurrence of sudden and uncontrolled hyperpyrexia associated with mania and followed by deep coma, circulatory collapse and other symptoms closely resembling those of shock. This condition was seen three times in each group with an incidence in the mild and severe treatments respectively of 0.36 per cent and 1.76 per cent. In the three instances occurring during mild treatments the uncontrolled temperature rise was moderate, the collapse was less profound, and recovery was more prompt than in the cases with severe treatments. The affected patients receiving mild treatments had repeated subsequent treatments without untoward results. The sequence of events as they occurred in a patient who was being treated for gonorrhea was as follows: the patient's temperature had been between 106.8°F and 107.2°F for 40 minutes when muscular twitchings were noted, his temperature rose to 107.8°F in five minutes despite the fact that both cabinet doors had been opened. He was removed from the cabinet promptly, an electric fan was directed upon his body and he was kept wet with tepid water. His temperature continued to rise, he was pulseless, his lips were pale, and he was in deep coma. His heart sounds were inaudible, and he had an involuntary bowel movement. After adrenalin was given intramuscularly, his heart sounds became audible, the heart rate was 200, but no peripheral pulse could be felt. His temperature reached 109°F . He was given 50 c.c. of 50 per cent glucose solution intravenously. A half hour later his pulse improved, the blood pressure rose to 78 over 50, the temperature fell to 107° , he recovered from his coma but was completely disoriented. After another half hour his temperature was 104° , he became oriented, and suddenly had copious projectile vomiting, severe abdominal cramps and a rigid abdomen. The vomiting and rigid abdomen persisted for about 72 hours. He was observed closely as a patient with suspected intestinal obstruction, but he made an uneventful recovery without operation. Another patient, treated for gonorrhea, started with mania followed by deep coma and circulatory collapse. He had a severe epileptiform seizure lasting about five minutes. Upon recovery he was found to have right facial paralysis and aphasia, both of which symptoms disappeared within about 10 days. It is such experiences, rare though they be, which remind us of the seriousness of fever therapy at high temperature levels.

SUMMARY

Attempts at artificial fever production for the past 50 years have resulted in the development of many successful methods based upon various principles. The complications and hazards of fever therapy depend primarily upon the height and duration of the fever produced.

The complications and hazards observed in 1000 consecutive fever treatments given with the Kettering Hypertherm have been analyzed. Two types of treatment were given: (1) mild treatments, given chiefly to patients with various chronic diseases, limited to a body temperature of 105° F, and never maintained longer than five hours; and, (2) severe treatments, given to patients with gonorrhea, in which a body temperature of 106° F to 107° F was maintained for five to seven hours. The proportionate number of treatments which had to be discontinued, the incidence of skin burns produced, the incidence and severity of circulatory collapse were much greater in the severe treatments than they were in the mild treatments. The incidence of anorexia and excessive loss of weight after mild treatments was greater than after severe treatments. The incidence of herpes was unaffected by the severity of the treatments.

Despite the complications and hazards observed, the production of artificial therapeutic fever, with body temperatures even to 107° F maintained for five hours or longer, under proper conditions of supervision has proved to be a practical and satisfactory procedure.

LIVER FUNCTION IN RHEUMATOID (CHRONIC INFECTIOUS) ARTHRITIS; PRELIMINARY REPORT*

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DURING the past few years, much interest has been focused on the subject of decreased dextrose tolerance in acute infectious diseases. Williams and Dick¹ found a decreased tolerance in 41 per cent of patients and they also found a similar disturbance in carbohydrate metabolism in experimentally induced toxemia in animals. Their paper contains an excellent review of the literature.

Two explanations have been offered for the "diabetic" type of dextrose tolerance curves obtained in these conditions. Some authors^{1,2,3} ascribe it to lack of endogenous insulin caused by the functional impairment of the islets of Langerhans, while others^{4,5,6} maintain that it is due to an interference with the action of the available insulin, whether of endogenous or exogenous origin. These interpretations are based upon the belief that the normal dextrose tolerance curve is dependent upon an increase in the circulating insulin consequent to pancreatic stimulation from the dextrose administered. However, Soskin et al.⁷ have shown recently that a normal dextrose tolerance curve may be obtained in a completely depancreatized dog which is receiving an amount of insulin and dextrose just sufficient to maintain the blood sugar at a constant level. They also state⁸ that "an animal in this condition shows a hypoglycemic reaction at least as great as that of a normal dog following the cessation of prolonged administration of dextrose." They reason, therefore, that the normal reactions to the administration of dextrose do not require the secretion of additional insulin and that the abnormal curves observed in toxemia do not result from the lack of extra secretion.

From the results of simultaneous observations on the sugar content of the blood entering and leaving the liver during tests for dextrose tolerance, they⁷ concluded that "in the presence of a sufficiency of circulating insulin, but not necessarily of an extra secretion from the pancreas, the normal liver responds to administered dextrose by decreasing its own output of blood sugar which it previously had been supplying from its own resources." Their findings have been substantially confirmed by Tsai and Yi⁹ who calculated the quantity of sugar entering and leaving the liver by means of a flowmeter. Soskin et al.^{7,8} then concluded from their experiments that

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the toxemia probably interferes with the homeostatic mechanism of the liver as postulated above, through its effect on the liver itself. Sweeney and his associates^{5,6} believe that the toxemia acts, not by suppressing the endogenous insulin supply, but rather by interfering with the function of insulin, whether of endogenous or exogenous origin. Yannet and Darrow¹⁰ during the course of intoxication in rabbits produced by the intravenous injection of diphtheria toxin did not find any gross disturbance in carbohydrate oxidation. They did observe changes in the liver, however, and concluded that the observed changes in carbohydrate metabolism were due to a disturbance in hepatic function. Soskin et al¹¹ found that the intravenous injection of diphtheria toxin into normal dogs caused a definitely prolonged dextrose tolerance curve, while the injection of boiled toxin was without effect. In depancreatized dogs, the curves after the injection of toxin were even more abnormal than in normal animals, although the preliminary curves were quite normal. They concluded, therefore, that abnormal dextrose tolerance occurring in cases of toxemia was due to the effects of the toxemia on the liver and not on the pancreas. This is not surprising when one considers that, incidental to its function of detoxication, the liver bears the brunt of the toxemia which accompanies acute or chronic infection. Because of these observations, a study was begun in 1932 to determine whether any disturbed liver function occurred during the toxemia of rheumatoid (chronic infectious) arthritis.

Patients were selected on admission to the clinic and divided into severe, moderately severe and mild rheumatoid arthritis. Only those patients with classical symptoms of rheumatoid arthritis were included in this study.

The Azorubin S test was selected for the liver function test. Tada and Nakashima¹² in a study of 62 dyes found that, while other dyes were excreted in large part by the kidneys as well as by the liver, 95 per cent of intravenously injected Azorubin S was eliminated by the liver and only 5 per cent by the kidneys. Using the duodenal tube, they found that in normal persons the dye appeared in the bile in 17 minutes. Weiss¹³ concluded that this test seemed to measure the functional capacity of the liver quite as well as the Rosenthal test.

TECHNIC OF THE AZORUBIN S TEST

The duodenal tube is passed in the morning on a fasting stomach. When the tube reaches the duodenum and a yellowish-brown bile begins to flow, 4.0 c.c. of a 1.0 per cent solution of Azorubin S are injected intravenously. Five minutes after the injection of the dye, 40 c.c. of a 25 per cent magnesium sulphate solution are injected through the duodenal tube. In normal individuals a characteristic, deep red bile appears about 17 minutes after the injection of the dye.

From 15 to 30 minutes was accepted as the normal appearance time of the dye. Less than 15 minutes and more than 30 minutes indicated liver

dysfunction in proportion to the decreased or increased appearance time of the dye. The interpretation of liver dysfunction in patients with a decreased appearance time is based on the findings of Whipple, Peightal and Clark¹⁴ who reported a hypersecretion of phenoltetrachlorophthalein with small doses of phosphorus which they attributed to the irritative effect of the phosphorus on the parenchyma of the liver. Soskin and Mirsky,¹⁵ working with dogs in which liver damage had been produced by the intravenous injection of diphtheria toxin, found three different stages of dextrose tolerance depending upon the extent of liver damage. They concluded that Stage I (early liver damage) "is characterized by an early decline in the inhibitory effect exerted by the administered sugar so that the liver fails to decrease its own supply of blood sugar as rapidly as normal and a 'diabetic' type of tolerance curve results."

ANALYSIS OF 100 CASES

In four cases the appearance time was less than 10 minutes, in 32 it was 10 to 15 minutes, in 45, 15 to 30 minutes, in four, 30 to 35 minutes, in nine, 35 to 40 minutes, and in six, over 40 minutes. Of the entire number studied, 55 per cent showed some liver dysfunction. In 15 patients with osteo-arthritis, four (28 per cent) showed liver dysfunction, compared to 55 per cent with rheumatoid arthritis. However, the series of patients with osteo-arthritis is too small to permit definite conclusions. The following patients with rheumatoid arthritis showed liver dysfunction: 27 of 34 severe cases (73 per cent), 21 of 44 moderately severe cases (47.5 per cent), and seven of 22 mild cases (25.25 per cent).

From these figures it would appear that to some extent the liver dysfunction is parallel to the severity of the disease. There was no relation between the duration of the disease and the liver function. Although no control series is reported here, liver dysfunction in patients with severe rheumatoid arthritis is so much more frequent than in patients with mild rheumatoid arthritis (73 per cent compared to 25.25 per cent) that it suggests that liver dysfunction in such a high percentage is an abnormal finding. Cytological examinations of the bile in 50 cases showed abundant leukocytes in 24, or 48 per cent. Some patients with achlorhydria responded to stimulation with histamine or neutral red. Many of them showed an abnormal liver function test.

SERUM PROTEINS

A quantitative determination of serum proteins was made in patients showing liver dysfunction. In most cases, there was a slight reduction of the total serum protein and a reversal of the albumin-globulin ratio. This occurred both in cases having a rapid dye appearance time and in those having a delayed appearance time. For example in one case of rheumatoid arthritis the dye appeared in 37 minutes, the total serum proteins were 6.07

per cent, albumin, 3.5 per cent, globulin, 2.57 per cent, and the ratio, 1.36. In another case, the dye appeared in 12 minutes, the total serum proteins were 6.27 per cent, albumin, 3.81 per cent, globulin, 2.46 per cent, and the ratio, 1.55. A few cases with a normal Azorubin S test gave a reduction of the serum protein and a reversal of the albumin-globulin ratio. In the majority of cases studied, there was a correlation between liver dysfunction, the reduction of serum proteins and reversal of the albumin-globulin ratio.

TREATMENT OF LIVER DYSFUNCTION

Where the bile showed an abundance of pus cells, cocci, etc., 10 c.c. of choleval were given intravenously twice weekly. Usually six to eight injections were given, depending upon the improvement of the cytology of the bile. When choleval was omitted, decholin-sodium was given intravenously in order to increase biliary drainage but, where a number of injections was given, a 5 per cent solution was used in order to prevent excessive secretion in those patients who may have had partial obstruction. This preparation has a tendency to increase biliary secretion and thus increase the elimination of detritus from the biliary tract.

DIET

The diet was regulated according to the requirements of each patient. In some patients with liver dysfunction, a high carbohydrate diet was given, and frequently there was a gain in weight and improvement in the constitutional symptoms. As far as could be ascertained, this did not produce harmful effects. This agrees with the recent reports of Bowen and Lockie.¹⁶ A high protein diet was used in those patients showing nutritional edema. In view of the lowered values for serum proteins and the reversed albumin-globulin ratio in rheumatoid (chronic infectious) arthritis, noted previously by Davis¹⁷ and confirmed by us, it is suggested that the diet be adjusted to conform with the requirements of each individual patient.

DISCUSSION

A long series of papers has appeared on the relation of the liver function to plasma proteins. Kerr, Hurwitz and Whipple^{18, 19, 20} noted a regeneration of serum proteins following a plasmapheresis, the globulin being replaced more rapidly than the albumin. They also noted that, after a 50 per cent depletion of serum proteins, regeneration took place in five to seven days. This is the time required for regeneration of the liver cells after hepatic necrosis produced by carbon tetrachloride. Recently, Whipple and his associates^{21, 22} have given support to the theory that the liver is intimately concerned in the formation of serum proteins. The literature on the relation of hepatic disease to serum proteins has recently been reviewed by Snell.²³

It has frequently been reported that, in advanced chronic hepatic disease, there is often a moderate reduction in the total serum protein. This reduction occurs mostly in the albumin fraction with reversal of the albumin-globulin ratio. In the less advanced cases albumin may be only moderately reduced but globulin may be increased. Rowe²⁴ believed that infection is probably responsible for these findings. Snell²³ concluded that "one of the fairly constant effects of parenchymatous hepatic disease is reduction in the serum albumin and reversal of the albumin-globulin ratio, that these changes are most probably related to deficient production of protein by the liver, and that for this reason they may have some diagnostic and prognostic significance, and finally, that the serum albumin is often at or near a level which makes the production of ascites and edema relatively easy." His work is in accord with that previously reported by Myers and Keefer²⁵.

Davis¹⁷ found a definite reduction in the serum albumin, a rise in the serum globulin, and a reversal of the albumin globulin ratio in all cases of severe rheumatoid arthritis. Although a greater change occurred in those cases classed as severe rheumatoid arthritis, less severe cases also showed some change. It is interesting to compare his findings in normal cases with his reports on one case of tumor of the liver, one of acute cholecystitis, and one of pernicious anemia, all of which may have had liver involvement. The mean findings in these three cases were albumin, 4.05 per cent compared with 4.70 per cent in the normal group, globulin, 2.94 per cent compared with 2.26 per cent in the normal group, and the albumin-globulin ratio, 1.38 compared with 2.12 in the normal group. Although the degree of change was less, the findings in these three cases were similar to those observed in rheumatoid arthritis.

In view of the findings of Myers and Keefer²⁵ and Snell²³ of the reversal of the serum albumin-globulin ratio in liver disease, and of the present findings of liver dysfunction in 73 per cent of cases with severe rheumatoid arthritis, it is reasonable to assume that in most instances the changes in the serum proteins mentioned above and those also found by Davis¹⁷ in rheumatoid arthritis may have been due to liver dysfunction.

Snell²³ stated that the principal effects referable to a reduced albumin content of the blood serum of patients with hepatic disease are related to the production of edema and ascites. He believed that, although the "edema level" (4 to 5 gm per 100 cc) for the total serum proteins is not often reached, the disproportionate reduction in the serum albumin may reduce the osmotic pressure of the blood serum sufficiently to produce transudation, especially in regions where venous stasis occurs. Wells and his collaborators²⁶ have shown that, by direct measurement, the specific osmotic pressure of serum is a linear function of the concentration of albumin, the globulin content being relatively unimportant. It must be remembered, however, that there are other factors which may play a rôle in the causation of edema and ascites and that the lowered serum albumin may be only a contributing

factor The above may offer some explanation for the edema found in some cases of rheumatoid arthritis and possibly for the many varied clinical syndromes appearing in this protean disease It is also further suggestive evidence that rheumatoid arthritis is infectious in character

CONCLUSIONS

1 Liver dysfunction, as determined by the rate of excretion of Azorubin S, was present in 55 per cent of 100 patients with rheumatoid (chronic infectious) arthritis

2 Liver dysfunction occurred with greater frequency in patients with severe than in those with mild rheumatoid arthritis

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A MEDICAL POET LAUREATE, ROBERT BRIDGES, M D , POET LAUREATE OF ENGLAND 1913 TO 1930¹

By COMMANDER LOUIS H. RODDIS, F A C P , *Medical Corps, United States Navy*

THE Poet Laureate of England holds an official position of peculiar dignity and honor, even though the duties are nominal and the salary somewhat remarkable—a barrel of wine and one hundred and twenty pounds a year. The title is obtained from the laurel or bay, in classical times the crown of the hero and poet, the lover being crowned with myrtle. In 1921, Professor Broadus published a study of the office of the Poet Laureate, almost the first investigation of the subject made, and there still remains for some minor poet or literary historian, the pleasant task of writing the lives of the Laureates. The list, omitting some doubtful and “volunteer” Poet Laureates, includes but sixteen names and as a matter of interest they are here given:

Ben Jonson
John Dryden
Thomas Shadwell
Nathan Tate
Nicholas Rowe
Lawrence Eusden
Colley Cibber
William Whitehead

Thomas Warton
Henry Pye
Robert Southey
William Wordsworth
Alfred, Lord Tennyson
Albert Austin
Robert Bridges
John Masefield

Only one medical man has held the title, Robert Seymour Bridges, who was born at Walmer, Kent, England, October 23, 1844. His parents were in more than easy circumstances, and he was educated at Eaton and Oxford. His college was Corpus Christi, where he graduated B A , with distinction, having still further distinguished himself as an oarsman. After a short period of travel on the continent he entered as a student at St. Bartholomew's Hospital from which he received his degree of M B , in 1874, and where he served as house physician. Having completed his service he was appointed casualty physician at “Barts,” as St. Bartholomew's has been known to generations of English physicians, and later was elected assistant physician to the Great Northern Hospital and to the Hospital for Sick Children in Grand Omond Street.

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This is the ninth of a series of portraits of medical poets. Those which have previously appeared in the ANNALS OF INTERNAL MEDICINE are: Joseph Rodman Drake, February 1929, Oliver Wendell Holmes, June 1930, Oliver Goldsmith, May 1932, Wm. Savage Pitts, January 1933, Lieutenant Colonel John McCrae, June 1933, Dr. Richard Shuckburgh, June 1934, Johan Christoph Friedrich Schiller, March 1936.

In 1878 he published a paper in the St Bartholomew's Hospital Notes, "An Account of the Casualty Department," in which he recorded his experiences as admitting physician. From nine o'clock until twelve noon he spent interviewing patients and sending them to the appropriate clinical outpatient departments for treatment. In a year he saw 30,000 patients, two-thirds of these new cases. His whole article gives a clear and striking picture of the casualty work of this great London Hospital more than half a century ago. He also contributed a report on a case of rheumatic fever, treated by splinting the affected joints with good results. His third contribution to literature was a semi-humorous poem of 558 lines, written in Latin and describing the foundation of St Bartholomew's Hospital, with characterizations of its staff.

"Carmen Elegiacum Roberti Bridges de Nosocomii
Sancti Bartholomaei Londiniensi"

Such evidences of the classical learning of the author indicate how the medical tradition for classical scholarship established by Linacre, Caius and Heberden was carried on into the Victorian age.

Bridges had begun to write verse at an even earlier period, and his first volume of poetry appeared in 1873. From then until his death he continued to publish isolated verse, dramas, and successive volumes of poems. His last work, "The Testament of Beauty," appeared on his eighty-fifth birthday, so that his period of productive activity as a poet covered 56 years.

A number of physicians have distinguished themselves in art, literature and science, and still continued in the active practice of their profession. Medicine, however, is a jealous mistress, and many more have forsaken her to follow another love. This was the case with Bridges, and in 1882 he gave up his practice to devote himself more and more to poetry and scholarship. The possession of abundant private means enabled him to follow his inclinations in this respect without any difficulty. It is of interest to note that "Prometheus the Fire-Giver," one of the most ambitious of his earlier works, was published in 1883, the year after he had definitely abandoned Medicine.

To the end of his long life he remained a poet and scholar. Few other English poets have been such profound students of the art of versification or have admired, studied, experimented and exalted the use of English as a medium of expression. He was the author of a book on "Milton's Prosody," a penetrating study of rhythm and sound in English poetry. He was also one of the founders of the Society for Pure English and was the general editor of its publications. S P E Tract No 9 had as joint authors, Dr Bridges and Dr Cuthbert Morton. It was on the language of anatomy, so we see here his return to a medical theme. The object of the pamphlet was "to condemn the action of those who are moving to introduce a formal Latin international terminology into the British Schools of anatomy on the false note that it will be of service to international science." This was a plea

to use an English terminology His last work, "The Testament of Beauty," is an attempt to introduce a radical change in English spelling Indeed, Bridges was as distinguished in the field of English scholarship as he was as a poet This preoccupation with scholarship, and what one might call the technical feature of versification, led to many of his poems giving an impression of careful design rather than spontaneous inspiration This quality of his work is well shown in one of his most often quoted poems, "London Snows"

"When men were all asleep the snow came flying,
In large white flakes falling on the city down,
Stealthily and perpetually settling and loosely lying,
Hushing the traffic of the drowsy town,
Deadenng, muffling, stifling, its murmurs failing,
Lazily and incessantly floating down and down"

Of the two eternal themes of the poets, Love and Nature, Bridges was concerned primarily with the latter His love poems are few and justly criticized as lacking in passion and power Some of these, however, are not lacking in a deep and simple tenderness, as in this

"When death to either shall come,
I pray it be first to me,
Be happy as ever at home,
If so, as I wish, it be

Possess thy heart, my own,
And sing to the child on thy knee,
Or read to thyself alone,
The songs that I made for thee

Bridges has well carried on the tradition of English poetry as a mirror of the natural beauty of the English countryside, and has often in his verse celebrated

"Fair England in Her Pastoral Dream"

Here is a stanza worthy of Spencer

"There is a hill beside the silver Thames,
Shady with birch and brush and odorous pine,
And brilliant underfoot with thousand gems
Steeply the thickets to his floods decline"

The flowers, beloved of all the poets, are often found in his verse

"Pansy and Poppy-seed
Ripened and scattered well

And silver Lady-smock
The meads with light to fill,
Cowslip and Buttercup,
Daisy and Daffodil"

The appointment of Bridges as Poet Laureate in 1913, as the successor of Alfred Austin, was a great surprise to many. Though recognized as a poet and scholar of high rank, he was not well known to the general public who would have welcomed some more popular poet, as Kipling or Alfred Noyes. Kipling at the time was the most famous, as he was the most



Courtesy of Alfred Knopf, Inc., N. Y.

ROBERT BRIDGES

national of the living English poets. None of the others had written one poem which all people knew, while he had written a dozen. It is said that he was not favored as a royal poet because of reference to Queen Victoria as the "Widow of Windsor."

The appointment, however, did not lead to as much criticism as was received by his predecessor in office. King Edward had a very poor opinion of the work of Alfred Austin, and in a letter to Lord Salisbury (quoted in

Sir Sidney Lee's Biography of Edward the Seventh) the King said, "I always thought that Mr Austin's appointment was not a good one, but as long as he gets no pay it would, I think, be best, to renew the appointment in his favor" A little later he forwarded some of Austin's poetry to Salisbury and refers to it as "trash"

During the war there were remarks on the absence of war poetry on the part of the Laureate He wrote, however, a number of war poems which were published anonymously These were collected in 1920 in a volume entitled, "October and Other Poems" The supposed silence of the Laureate during the war led a Member in the House of Commons to inquire if the Poet Laureate should not be officially requested to "earn his butt of sack"

"The Testament of Beauty," Dr Bridges' last work, was published on his 85th birthday and attracted more popular attention than any of his other poems This was partly due to his adoption of simplified spelling "There" became "ther," "captive" became "captiv," "will" became "wil" Silent letters are almost entirely dispensed with throughout the poem of 190 pages It excited a great deal of controversy as do all such innovations, the more so that it was the work of the Poet Laureate and dedicated to the King One line in it, "wher ther is any savagery, thei wil be war," was taken as an example of his simplified spelling and little was said in the press accounts and reviews of the poetical merit of the work

Dr Bridges received many honors other than that of Laureate Oxford is only one of many universities that bestowed academic distinctions upon him He was made Doctor of Laws and a Doctor of Literature The Order of Merit, one of the most prized decorations, granted only for pre-eminence in art, literature, military affairs, and statesmanship, was bestowed upon him by the Sovereign In 1920 he was elected to Fellowship in the Royal College of Physicians

He died at his home, Chiswell House, Boars Hill, Oxford, April 21, 1930 He maintained the tradition of age among Poet Laureates by living for 85 years His three predecessors were Austin, who died at 79 years, Tennyson at 81 years, and Wordsworth at 80 years, an average of 80 years

There is an interesting story told of Bridges and his successor as Laureate The doctor was fond of bicycling, and on one occasion he had a puncture in his front tire, on the slope of Boars Hill just at dusk, and was assisted in the repair of the tire by John Masefield

Bridges was a handsome man and distinguished in appearance He looked the part of a poet and a poet laureate The portrait which illustrates this article shows him seated in his garden, a fitting picture as he was a lover of gardens and flowers and celebrated them repeatedly in his verse Another well known picture of the poet shows him seated at a piano, presented to him by admirers on his eightieth birthday Like so many poets and physicians he was an excellent amateur musician

CASE REPORTS

"ABDOMINAL INTERMITTENT CLAUDICATION" AND NARROWING OF THE CELIAC AND MESENTERIC ARTERIES "

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DEPRIVATION of the blood supply to the viscera is important among the causes of abdominal pain. The effects of sudden vascular occlusion are dramatic and well known. More obscure are the symptoms and pathology of gradual occlusion. Since the literature heretofore has treated these in a very stepmotherly fashion, the correlation of available clinical and pathological data may be of value.

CASE REPORT

A spinster of 76 was admitted to the medical ward complaining chiefly of abdominal pain after eating. She had been in good health until about six months before admission. At this time she began to experience numbness in the left calf upon exertion, tingling sensations in the fingers, and constant tinnitus. The abdominal pain began three months before admission. Immediately upon the ingestion of any food except water and fruit juices there would appear a sharp steady pain in the region of the umbilicus radiating to the symphysis pubis, left lower quadrant and back. The pains would last 5 to 30 minutes and were followed by a constant slight dull ache in the epigastrium. On two occasions she had been nauseated and had vomited thin colorless material. One week before admission she had had a watery diarrhea of two days' duration. She thought that her stools had been black at times. There had been no abdominal distention. On account of the pain her diet had been entirely fluid and she had lost a considerable but indeterminate amount of weight.

Upon physical examination the weight loss was apparent in the dryness and looseness of the atrophic skin. Subcutaneous tissue was practically absent. The rectal temperature was 99.8° F, the pulse 72 and the respirations 18. There was marked evidence of arteriosclerosis: the retinal vessels were thickened and tortuous and the arteries of the extremities were firm cords. Pulsations were appreciable in the right femoral and dorsalis pedis arteries, absent in the left. In the right thigh the blood pressure was about the same as that in the right arm (200/80), but in the left thigh it could not be determined. This extremity was definitely cooler than the right. Its calf and thigh diameters were, however, the same as those of the right. The apex impulse of the heart was best palpated in the fifth intercostal space 7 cm from the mid-sternal line. The rhythm was regular and the sounds were of fair quality with accentuation of the aortic second sound. A loud harsh systolic murmur was heard at the apex and a high pitched blowing diastolic at the base, most audible at the left sternal border. Examination of the chest revealed no evidence of pulmonary disease.

The abdominal wall was extremely lax. In the region between umbilicus and mid-epigastrium just to the left of the vertebral column most observers palpated a firm

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but vaguely defined, immovable, pulsating mass No other masses were felt There were no other notable findings in the physical examination

Guaiac tests of the stools were positive on several occasions No gross blood or "tarriness" was observed The non-protein nitrogen of the blood was 39 mg

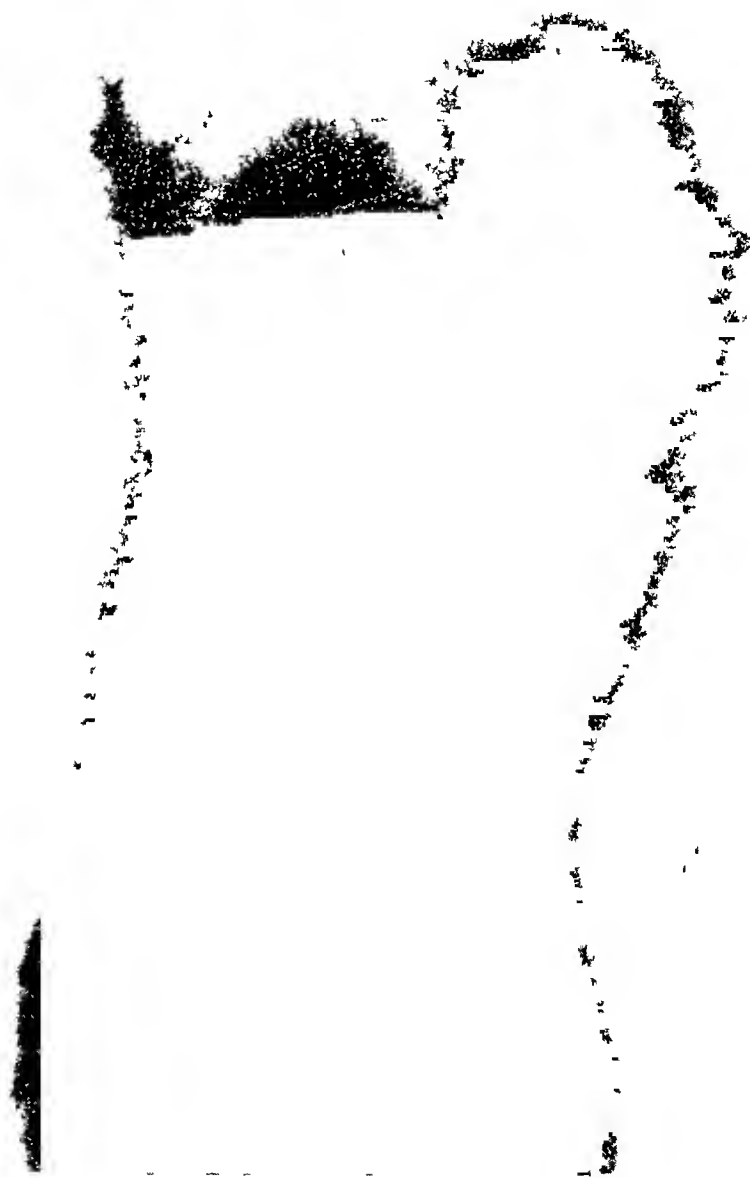


FIG 1 Roentgenogram Calcification of aorta

per 100 c c The Kahn test was negative The red blood cells numbered 4,300,000 per cubic millimeter with 90 per cent hemoglobin and the white blood cells 13,000 with 84 per cent polymorphonuclears, 14 per cent lymphocytes and 2 per cent L M The urine, except for the presence of 15 to 20 white blood cells in the low power field, was negative

At this time the recorded diagnoses included generalized arteriosclerosis with hypertension, and occlusion of the left iliac artery. The pain and abdominal mass were variously interpreted as due to aortic aneurysm, carcinoma of the stomach, pancreas or intestine, or to mesenteric vascular occlusion. Roentgenographic examination demonstrated marked calcification of the abdominal aorta, and the gastrointestinal

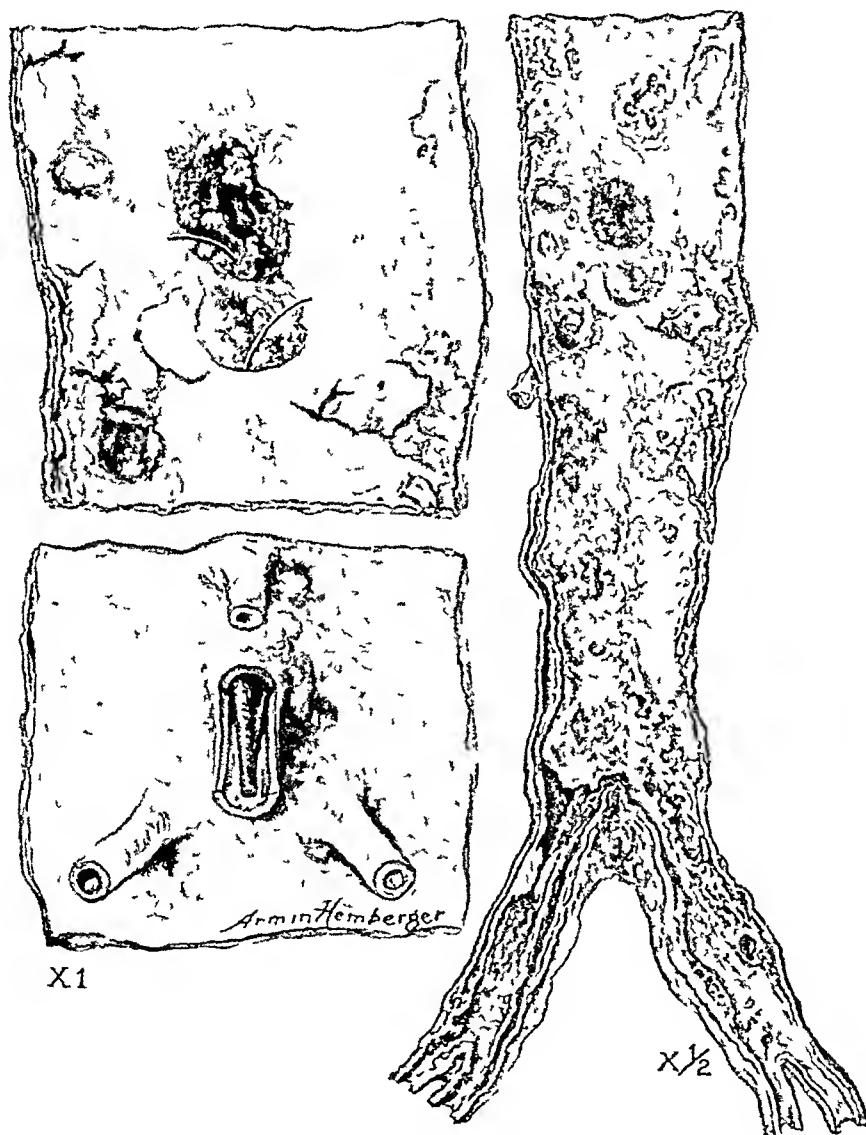


FIG 2 Ulcerative atherosclerosis of aorta with obstruction of celiac axis, left iliac and mesenteric arteries, thrombi in superior mesenteric and left iliac arteries

series revealed narrowing of the esophagus (interpreted as due to pressure of the aorta), atony of the stomach with 15 per cent retention of the gastric contents in six hours, and motor delay throughout the small intestine. Failure of the pylorus to dilate with peristalsis was thought compatible with the possible presence of a carcinoma in this region. Three stools in succession were guaiac positive. Nine days

after admission the patient vomited 300 c.c. of material resembling coffee grounds which was weakly positive for guaiac. These findings and the patient's great distress unrelieved by medical therapy induced the decision to perform an exploratory laparotomy.

At operation the peritoneal cavity was found to be devoid of exudate and the color of the intestines to be normal. On the lesser curvature of the stomach near the pylorus there was a tiny, firm zone slightly more vascular than the surrounding tissues to which the omentum was adherent. This was thought to be the serosal aspect of a small ulcer. The abdomen was then closed without further manipulation and the patient was returned to the ward in good condition. Soon thereafter, however, the blood pressure began to fall and the patient died 18 hours after operation despite supportive measures.

At postmortem, incision exposed dull, dark gray peritoneal surfaces. Fibrin covered the intestines, stomach and omentum, particularly at the site of operation. About 100 c.c. of foul dark purple fluid were collected in the right paracecal fossa and pelvis. The serous surfaces of the stomach and inferior surface of the liver were dull gray, those of the entire small intestine and proximal half of the large were dark purple. A loop of ileum adherent to the posterior wall of the bladder was almost black, and so soft that it tore easily in a gentle attempt to loosen the adhesion. The entire gastrointestinal tract was distended with dark red, malodorous fluid.

The mucosa of the stomach was gray, opaque and rugated in the usual fashion. Ulcerations were not found at any point and the vascular area observed at operation did not overlie any mucosal lesion. The pyloric layer of muscle was, however, unusually thick. Microscopic sections showed no evidence of carcinoma. Histologically the gastric mucosa was poorly preserved on account of postmortem change. The wall of the small intestine was so soft as to rupture readily in response to slight stress. A few small superficial ulcers were encountered in the lower ileum. Elsewhere in the ileum and in the large intestine the mucosal surface was opaque and gray-green but not ulcerated. The lower segments of the descending colon and sigmoid were of the usual appearance. The appendix was only 2 cm. in length and teat-like in shape. Its lumen was obliterated. Microscopically the mucosa of the small intestine had undergone complete necrosis. There was marked congestion of the vessels and hemorrhages were prominent at many levels. Cellular reaction was slight and of the polymorphonuclear type. Liver and pancreas grossly and histologically showed no evidence of infarction.

The aorta throughout its length was tile-hard and stiffly maintained its shape when placed upon the table. A remarkable gritty resistance was met in attempting to open the vessel from the rear. The intima in many places was raised by yellow, opaque atheromatous material. Elsewhere it had become superficially ulcerated or infiltrated with calcium now of oyster-shell consistency. About the mouth of the celiac axis was deposited a rosette of very hard material which virtually obliterated the ostium. Just distally, although thick-walled, the vessel was widely patent. The mouth of the superior mesenteric artery likewise was narrowed to an opening of pin-point size by a hard incrustation in its wall. A firm, fresh, laminated, red and gray thrombus completely obstructed the proximal 5 cm. of the vessel. Its branches were dissected and found to be patent although thickened. The inferior mesenteric artery was firm-walled and neither increased nor decreased in caliber. The lumina of the left common and external iliac arteries were reduced to mere crescentic slits because of tremendous thickening of the intima. This consisted of eccentrically split laminae of hyaline connective tissue patchily infiltrated with calcium. Calcification of the irregular media was also prominent. A fresh thrombus partially occluded the left common iliac artery. The corresponding vessels on the right showed similar changes in lesser degree. Their lumina were not obstructed.

The heart weighed 313 gm. It had a deep fatty layer within which the coronaries were palpable as tortuous cords of wire-like firmness. Multiple sections showed marked encroachment upon the lumen by atheromatous plaques, many of which were calcified. Occlusion was at no point complete and no thrombi were found. Calcium containing, hyalinized intimal and medial plaques were demonstrated histologically to have reduced the lumina to narrow channels. In the deeper intimal and medial layers copper-brown refractile hemosiderin granules were evidence of organized hemorrhage. The myocardium, particularly that of the apex and roots of the papillary muscles, showed a moderate degree of fibrosis. There was no evidence of infarction. The aortic valve was slightly thicker than usual but not calcified. Its leaflets were movable and, as far as could be determined, capable of competent closure.

SUMMARY OF CASE

In summary the history is that of a woman of 76 with marked evidence of arteriosclerosis who suffered from intermittent claudication in the left leg, and, latterly, with intermittent sharp abdominal pains coming immediately after eating. At postmortem there was found great narrowing of the left iliac vessels and of the celiac and mesenteric arteries at their mouths. Finally there was a recent thrombus in the last mentioned vessel with an infarct in the region of its distribution.

DISCUSSION

The analogy which the recurrent abdominal pain bears with intermittent claudication in the extremities or with syphilitic or arteriosclerotic narrowing of the mouths of the coronary arteries with angina of effort is plain. The symptom of pain coming so soon after ingestion of food may be accounted for on the basis of the presumably markedly reduced blood supply to the stomach. Occlusion of the celiac axis in the presence of a normal superior mesenteric artery may be without clinical or anatomical result. Collateral circulation usually finds ready access from the superior mesenteric system through the pancreaticoduodenal loop*. Specific instances are presented by Thane and by Hecht. In the present instance, however, the mouth of the superior mesenteric artery was strikingly reduced in diameter by calcium concretions. In addition there was clinical evidence of early cardiac failure (slight edema, breathlessness). These factors tend to reduce the efficiency of a possible collateral blood supply. The exact mechanism responsible for the abdominal pain when food entered the gastrointestinal tract, and for the motor delay is not clear although it has its analogies with intermittent claudication and with angina.

Although frequent reference is made in general articles (e.g., in the excellent one of Klein) to the occurrence of chronic abdominal pain in vascular disease specific examples with data relative to findings at postmortem are rare, nor do they supply sufficient material for the description of clear-cut clinical entities except in the broadest suggestive outlines. The accompanying tabular summary includes only those cases in the literature in which the findings at necropsy are stated.

* In the event of complete occlusion of the superior mesenteric artery, however, sufficiency of the collateral circulation is rare. There are, nevertheless, several striking exceptions. Nazari renders an account of six patients in whom old thrombi were seen to occlude the trunk of the superior mesenteric artery although the intestines were not infarcted. In one of these the inferior mesenteric artery was twice its usual size. A very remarkable example of a normal intestinal tract in the presence of obliteration of both the celiac and mesenteric trunks was described by Chiene in a dissecting room subject (1868). The blood supply was derived by anastomosis of the gastrointestinal vessels with greatly enlarged lumbar arteries.

Chronic Cases of Abdominal Pain Associated with Vascular Disease

Sex and Age	Chief Symptoms	Duration	Laboratory and Physical Findings	Course	Pathology	Source and Date
Female 48	Repeated attacks of severe pain in the right hypochondrium Profuse diarrhea, "coffee ground" stools Numbness of left leg	8 mos "of late"	Abdominal tenderness and distention Visible peristalsis Cangrene of left foot	Death soon after amputation of left leg	Laminated clot about the mouth of the superior mesenteric artery Entero colic and entero-enteric fistulas Thrombosis of left common iliac artery and vein	Howse 1878
Male 40	Intense abdominal neuralgia	5 yr		Found unconscious	Calcified mesenteric lymph nodes compressing the trunk of the superior mesenteric artery Thrombosis of superior mesenteric artery Hemorrhagic infarct of intestine	I epine quoted by Adenot 1890
Female 55	Constipation relieved only by enemata Pain in epigastrium, right hypochondrium and umbilicus, recently of special intensity and coming after meals Almost continuous pain in the lower abdomen	5 yr 4 yr To 6 mo before admission Past 6 mo	Vital signs normal Abdomen, soft, sensitive in the epigastrium	Operation gall-bladder showing slight chronic cholecystitis removed No relief of symptoms Death suddenly 1½ mo after operation	Complete obliteration of superior mesenteric artery by an old organized thrombus Fibroid hemorrhagic peritonitis Infarct of small intestine	Schnitzler 1901

Chronic Cases of Abdominal Pain Associated with Vascular Disease—*Continued*

Sex and Age	Chief Symptoms	Duration	Laboratory and Physical Findings	Course	Pathology	Source and Date
Male 55	Pain in region of umbilicus and in right lower quadrant, severe distention 1½ hr after each heavy meal Constipation relieved by enemata	2 years Several remissions Present attack 3 mo	Marked distention of abdomen 2 to 3 hrs after eating	Death 1½ days after exploratory laparotomy	Extensive arteriosclerosis of superior and inferior mesenteric arteries including their finer branches, distention of entire gastrointestinal tract Peritonitis	Ortner 1902
Male 41	Abdominal pain, nausea and feeling of rapid fullness after eating Admitted in emergency on account of attack of extremely severe abdominal pains, blood in vomitus and stools	21 months	Wassermann reaction positive Normal gastric analysis Pallor, sweating Slight diffuse distention Slight muscular guarding W B C 18,000 Temp 38.2°C	Operation performed under diagnosis of perforated gastric ulcer Resection of 1 meter of upper ileum Patient died soon after	Thrombi, sessile upon ulcers of aorta, one of which acted as a flap valve over the mouth of the superior mesenteric artery	Storring 1934

Clinically pain was the most prominent symptom. The duration varied from eight months to five years. Most often it was in the periumbilical region or right side. In three instances it was stated to be associated with ingestion of food—appearing one to three hours later. Moynihan remarks that “the greater suffering caused by heavy meals as compared with the less suffering after light meals is most significant.” Distention accompanied the pain to a striking degree in one patient, and a feeling of fullness and of nausea in another. Two suffered from diarrhea, but in two constipation relieved only by enemata was the characteristic symptom. Vomiting was rare. The most constant recorded features on physical examination were abdominal tenderness (four patients) and distention (three patients). The abdomen was soft to palpation.

The anatomical changes were diverse. In one case a laminated clot narrowed the mouth of the superior mesenteric artery, in another a thrombus sessile upon an atheromatous ulcer acted as an obstructing valve and in Schnitzler's patient an old thrombus completely occluded the trunk of the vessel. In one post-mortem examination calcified mesenteric lymph nodes were seen to compress the superior mesenteric trunk. In Ortner's case there was extreme arteriosclerosis of the superior and inferior mesenteric arteries including their finer branches. It is of interest that infarction of the small intestine with peritonitis was the terminal event in three of five recorded cases and also in the subject of the present report. Operation was followed by death in all of the four patients on whom it was performed.

More difficult to interpret are the published clinical impressions without necropsy material (Gilbride, Meyer, Goodman, Hamburger). Their chief value is in the light that they shed on possible treatment. The clinical descriptions are in agreement with those summarized in the table. Gilbride emphasizes the tenderness of the abdominal aorta, the epigastric or umbilical pain that may increase during digestion, upon exertion, in association with emotional disturbances or upon assumption of the horizontal position. Remarkable is the relief reported to be obtainable with various vasodilators. Hamburger has used nitroglycerine in doses of gr 1/50 with success as has Gilbride. Buch and the latter recommend strophanthus and theobromine sodium salicylate.

Among the diseases to be considered in the differential diagnosis are the colics, renal, biliary, intestinal and that associated with plumbism, peptic ulcers, abdominal aneurysms, gastric crises of tabes, and above all carcinoma where the possibility of relief by surgery exists. True anginal heart disease with pain referred to the abdomen is usually accompanied by substernal pain (Buch). The use of vasodilators may serve as a therapeutic test, but all available physical and laboratory methods should be employed to rule out non-vascular disease.

CONCLUSIONS

The symptoms associated with abdominal arteriosclerosis, as shown by the five cases reported in the past and the present case, are usually of upper abdominal pain sometimes associated with the ingestion of food, abdominal tenderness and, to a lesser degree, distention and feeling of fullness. Either constipation or diarrhea may be present. Vascular disease should be more often considered in the differential diagnosis of chronic abdominal pain than heretofore. This is all the more important because of the great danger of operation in such

cases and the possibility of securing relief by the use of vasodilators. It is obvious that further study with careful clinical, roentgenographic, electrocardiographic and necropsy reports are necessary.

Note Since this paper has gone to press, another article on this subject has appeared DUNPHY, J. E. Abdominal pain of vascular origin, *Am Jr Med Sci*, 1936, cxcii, 109-113.

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PRIMARY PNEUMOCOCCIC PERITONITIS, RECOVERY OF THE ACUTE SEROUS TYPE FOLLOWING TYPE I SERUM TREATMENT WITHOUT SURGICAL INTERVENTION*

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PNEUMOCOCCIC peritonitis is comparatively uncommon and bears a grave prognosis. It is generally divided into two types, primary and secondary. The primary type is characterized by involvement of the peritoneum without any discernible focus of infection and it tends to run one of two courses. The most common course is an acute diffuse serous peritonitis that usually ends quickly in exitus. The second course results in a localized and circumscribed abscess of the peritoneum and is associated with a more favorable prognosis. In the secondary type of pneumococcic peritonitis we find an antecedent or coincidental source of infection, usually the respiratory tract, with subsequent development of peritonitis.

In primary pneumococcic peritonitis, the majority of cases have been treated surgically with a very high mortality, especially in the acute diffuse type. Lipschutz and Lowenburg¹ had a mortality of 100 per cent in a group of 13 cases reported in 1926.

In our review of the literature, recovery in a patient with the acute serous type of primary pneumococcic peritonitis, without surgical intervention, and with specific serotherapy has previously not been reported. The purpose of this paper is to report such a case with dramatic recovery following the therapeutic use of specific serum.

CASE REPORT

M M, female, aged five, entered the Beth Israel Hospital on January 6, 1935, complaining of abdominal pain and fever.

Past History. This included whooping cough at the age of 10 months, measles at the age of two years, pneumonia one year previously. The patient was known to be sensitive to various foods and had received diphtheria toxin and antitoxin immunization. There was a family history of bronchial asthma. According to the parents, the child developed an upper respiratory infection 10 days before admission, characterized by a slight non-productive cough, unassociated with temperature or malaise. Seven days before admission, the child complained of twinges of abdominal pain, not severe in nature, nor incapacitating. This episode was repeated five days before admission. Throughout this period she was up and about, attending school. During the evening prior to admission, the child complained of a "bellyache." On the morning of admission, she ate a good breakfast, and had no complaints, but in the afternoon she developed anorexia and lassitude and a temperature of 104.5° F by rectum. During the inspection of the throat the patient vomited for the first time. The vomiting was non-projectile in nature. In the afternoon the patient suddenly developed severe generalized abdominal pain and was found to be writhing in agony. These cramps continued intermittently until 6 p.m. The child became extremely toxic and was referred to the hospital.

* Received for publication June 17, 1936.

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Physical examination revealed a well developed, well nourished child with flushed face lying in bed, talkative and cooperative Temperature 105° F, respirations 30, pulse 150 The throat showed only mild injection without exudate The examination was otherwise negative except for a distended abdomen showing moderate involuntary spasticity most severe in the right lower quadrant By rectal examination, there was more tenderness in the right lower quadrant than the left

MM

Day of disease 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

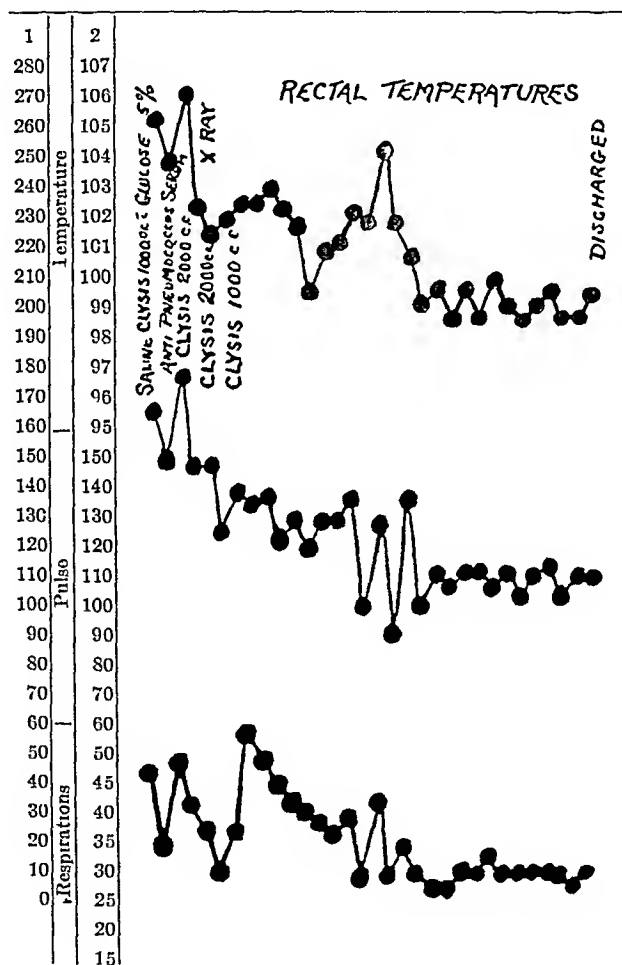
JANUARY
Day of month 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

CHART 1

Clinical Course Upon admission (evening of January 6, 1935) patient was put in high Fowler's position All fluids by mouth were restricted and the water balance maintained by an intravenous drip of 2.5 per cent glucose in normal saline solution Distension was controlled by flaxseed poultices and rectal tube Morphine sulphate gr 1/24 was given subcutaneously every three hours Admission blood culture (read after 14 hours' incubation) showed many colonies of gram positive diplococci On typing, this was found to be Type I pneumococcus The admission urine showed a

specific gravity of 1.036, v. s. t. of albumin, 2.5 per cent sugar, 3 plus acetone, one to three pus cells per high power field. The admission white count was 14,400 per c. c. The admission red count was 4,100,000 per c. c., hemoglobin 80 per cent. Throat smear on admission showed many gram positive diplococci and streptococci. Roentgen-rays of the chest were negative.

The next day (January 7, 1935), the temperature rose to 106.5° by rectum, pulse 172, respirations to 44. The patient was markedly dehydrated, wildly delirious, toxic and completely irrational. The patient was controlled by the constant care of extra nurses daily (two on a shift). Paraldehyde was given by rectum for restlessness. The white blood count rose to 18,400. Stool examination showed no blood on Guaiac test. The abdomen was definitely more spastic throughout with increased resistance in both lower quadrants where the patient also, in her more lucid moments, noted more pain on pressure. The heart and lungs were negative. During the evening the patient was started on antipneumococcus serum therapy as described in the chart. The intravenous drip of 2.5 per cent glucose in salt solution was continued and two clyses of 1000 c. c. of saline and glucose were also given.

On January 8, 1935 (the second hospital day), the day after the administration of serum, the abdomen was somewhat softer. The patient was rational, no pain was noted on pressure about the umbilicus. There was some tenderness in both flanks, however, and both lower quadrants. The temperature, pulse and respiration dropped to 102° (by rectum), 140 and 25, respectively. The intravenous use of serum was continued as described in the chart.

On January 9, 1935 (the third hospital day), the patient continued rational and became brighter, more cheerful and talkative. Intravenous drip was discontinued and the patient was allowed cracked ice and sips of water as desired. The intravenous use of serum was continued. The temperature remained about 102° rectally and the pulse went down to 130. The second blood culture was negative (no growth on culture media after nine days). The white count dropped to 9,100 per c. c. in the morning and to 7,700 in the evening. The patient's fresh blood serum agglutinated Type I and Type II pneumococcus microscopically. Type I pneumococcus was agglutinated in dilution of one to two only. On January 10, 1935 (the fourth hospital day) the patient developed a cough and hiccup on respiration. Roentgen-ray of the chest was negative. There was tenderness at the right and left upper quadrants. Respiration 48. (See clinical chart.) During the next four days the spasm and tenderness in the abdomen diminished so that there was some residual tenderness only in both lower quadrants. The abdomen became "doughy" to touch, abdominal distention was present and a fluid wave could be felt. Distention was controlled by flaxseed to the abdomen and by a rectal tube. The temperature remained 102° F rectally. The patient continued bright, talkative and cheerful. Fluids by mouth, up to three ounces at a time, were well tolerated. The final dose of serum (8 c. c.) was given intravenously. A third blood culture taken on this day proved to be negative. The patient's fresh blood serum showed complement in low titer as measured by activation of sheep cell hemolysis. Fresh blood serum agglutinated Type I and Type II pneumococcus microscopically and macroscopically. The serum agglutinated Type I pneumococcus in dilution of 1-4, but failed to agglutinate Type II pneumococcus. One liter of urine was concentrated to 5 c. c. From this an attempt was made to recover specific substances, but the alcohol insoluble material contained no substances which would precipitate Type I antipneumococcus serum*. The white count was normal. The urine showed no sugar, albumin or acetone, sediment negative.

On January 11, 1935 (the fifth hospital day) the patient continued to improve, the temperature remained about 100° F rectally, and most of the abdominal signs and symptoms disappeared. The white count was normal and the urine was negative.

* We are indebted for the performance of these tests to Dr. Maxwell Finland, who also assisted in directing the sero-therapy.

On January 12, 1935 (the sixth hospital day) the patient's temperature dropped to 98.6° F rectally in the morning. In the afternoon, the patient developed serum sickness, characterized by fever (104.4° F by mouth), arthralgia and rash. This subsided in four days. Further convalescence was uneventful with blood and urine normal and the patient was discharged on January 22, 1935, the sixteenth hospital day.

COMMENT

There have been many differing views regarding the mode of infection in primary pneumococcus peritonitis. The peritoneum may presumably become infected (a) through the gastrointestinal tract, (b) by way of the blood stream, (c) from the vagina through the fallopian tubes to the pelvic peritoneum. The evidence in favor of the transdiaphragmatic lymphatic route is meager. The direction of the lymphatic drainage in the region of the diaphragm has been shown to be upwards. There have been some proponents of the theory that pneumococci reach the peritoneum by egress from the intestinal tract. However, Jensen,² Wolfsohn,³ and McCartney and Fraser,⁴ were unable to produce peritonitis by feeding cultures of pneumococci to mice, even though the former demonstrated pneumococci in the intestinal wall. Obadalek⁵ and Koennecke⁶ concur in the belief that pneumococci in feces may produce peritonitis by contamination of the genital tract in females. Rischbieth⁷ and others advance the view that pneumococcal peritonitis is always secondary to a septicemia. Pneumococcal septicemia, however, is a very frequent concomitant of lobar pneumonia, which is very rarely complicated by peritonitis. Rolleston⁸ found 11 cases of peritonitis in 4454 cases of pneumonia, Rischbieth only one case in 6000 pneumonias and Elkin⁹ three in 1908 cases. Blake and Cecil¹⁰ were unable to produce pneumonia or peritonitis by intravenous injection of pneumococci, the animals dying of septicemia. On the other hand, Jensen¹ showed that pneumococci reached the blood stream in a rabbit a few minutes after intraperitoneal injection. These experiments were confirmed by McCartney and Fraser. Apparently other factors in addition to the mere presence of pneumococci in the blood stream are necessary to produce peritonitis. Peiser¹¹ suggested that the uninjured peritoneum was impermeable to the invasion of organisms from the blood stream. This may account for the increased frequency of peritonitis in association with nephrosis with ascites. McCartney and Fraser⁴ made a detailed study of the mode of infection and found no evidence in favor of either the hematogenous or enterogenous theories. They regard all cases of primary or idiopathic pneumococcal peritonitis as arising from the genital tract and of necessity therefore, limited to the female sex. In their study of 56 cases, they claim that the 12 cases occurring in boys were all of the secondary type. Barrington-Ward¹² and others, however, have reported cases in boys. In one case reported by Leonardo, the disease developed in a woman who had had an amputation of the uterus 15 years previously. Nevertheless, the overwhelming incidence in girls points strongly toward the genital tract as the chief source of infection with an occasional case arising via some other route.

Diagnosis. The primary type occurs most frequently in children between the ages of two and seven. The disease is usually characterized by an abrupt onset of severe abdominal pain, chiefly localized in the lower abdomen. Vomiting and diarrhea may occur, the latter sometimes associated with tenesmus. Hyperpyrexia, prostration, delirium and dehydration are other features. Cases

with a more chronic course have been reported with and without an associated intraabdominal localization of the purulent process. As a rule the more chronic type of case has a much better prognosis. A milder form with a spontaneous recovery has also been observed and described as an abortive type¹³. In suspected cases immediate blood culture is of paramount importance since many of these cases are associated with a pneumococcal septicemia. We have already mentioned that experimentally the blood stream shows the presence of organisms within a few minutes after intraperitoneal injection. Frequent smears from the culture medium should be made. As soon as organisms are discovered typing should be at once performed.

In the differential diagnosis one must consider chiefly acute appendicitis with or without perforation and subsequent peritonitis, and peritonitis due to the streptococcus. In most cases the diagnosis of appendicitis was made when the patients were first seen, and not until after an examination of the abdominal fluid at operation was the correct diagnosis made. In suspected cases abdominal fluid may be obtained by abdominal paracentesis. In 100 cases Neuhoff and Cohen¹⁴ demonstrated that this was an innocuous procedure. Other authors advocate puncture of the pouch of Douglas in females¹⁵. In some cases pneumococci have been found in vaginal smears.

An attempt to type the pneumococcus should always be made immediately irrespective of the source of the organism. There are no reliable statistics to indicate the actual frequency of the various types of pneumococci found in primary pneumococcal peritonitis. Prior to 1926, Leonardo¹⁶ found a total of 22 cases in the literature where the organisms were typed, 16 were Type I, 3 Type II and 3 Type IV. Since then the marked paucity of complete bacteriological studies has been striking, most of the authors being content with determining the generic organism.

The indefinite character of the patient's symptoms prior to admission precludes any estimation as to the time of onset of the peritonitis. This child had a history of a mild upper respiratory infection about a week preceding the onset of the peritonitis and examination of the throat failed to reveal any definite abnormality. The negative physical examination of the chest and the repeated roentgen-rays ruled out the lungs as the source of the infection. However, the patient's course was fulminating with hyperpyrexia during the day of entry.

The diagnosis was based upon (1) history of an upper respiratory infection (present in 90 per cent of the cases reported by Lipshutz and Lowenburg¹) (2) Onset of severe abdominal pain with signs of an acute "surgical" abdomen (3) Temperature that varied between 105 and 106.6° F rectally (4) Rapid prostration and delirium (5) Positive blood culture (Type I pneumococcus).

It was the unanimous opinion of all who saw the patient that surgical intervention was not indicated*, it was felt that her condition was so critical that an operation would be fatal.

In view of the presence of Type I pneumococci in the 14 hour blood culture immediate sero-therapy was instituted with the results indicated in the clinical course and in the chart.

Cases have been reported where a Type I pneumococcus was found at operation and sero-therapy was instituted after operation¹⁷. We have been un-

* Dr C G Mixter and Dr D D Berlin as surgical consultants and Dr E H Place as consulting pediatrician were all opposed to surgical intervention.

able, however, to find a case of primary fulminating pneumococcic peritonitis (i.e., acute serous type) treated solely by specific serum. In 1924, Struther¹⁸ stated that he "was able to find no information on the use of specific sera in pneumococcic peritonitis." Although Barrington-Ward suggested the use of specific serum in the outline of treatment, none of his cases had received serum. Fricke¹⁹ reported one case, an adult, of the more favorable chronic type, who was given serum and recovered without operation. He does not state how long the condition existed before giving the serum. The clinical condition of our patient was so critical and her response to serotherapy was so pronounced that it is unlikely that a spontaneous remission in the disease had taken place.

Serum Chart

1/7/35	9 30 p m	0 04 c c	of Massachusetts anti-pneum serum in left forearm intra-cutaneous
	9 36 p m		Wheal 6 mm not sharply demarcated and without pseudopods and 2.2 cm of faint erythema
	10 00 p m		No change Control negative
	10 00 p m	0 08 c c	Serum subcut in left infradeltoid region
	10 20 p m		No local reaction Skin test has faded completely
	10 30 p m	0 30 c c	Subcut over deltoid No reaction
	11 00 p m	0 80 c c	Subcut over deltoid No reaction
	11 30 p m	0 20 c c	Intramusc in deltoid No reaction
	11 55 p m	15 c c	Father's serum intragluteally No reaction
	12 00 p m	0 8 c c	Intramusc into deltoid
1/8/35	12 30 a m	0 5 c c	Intravenously, over at 12 38
	12 50 a m		Rash over left chest, face, body blotchy, no wheals
	12 50 a m		Respirations irreg, face slightly cyanotic Inspir and expir wheezes in right chest, prolonged expirations—P 150
	12 55 a m		Adrenalin 1/1000 0 3 c c intradeltoid
	1 00 a m		Resp regular, wheezes disappeared, rash almost completely faded T 1 30 a m 106.4
	2 30 a m		Blotchy rash re-appears on chest and abdomen No resp distress
	3 10 a m		Rash more punctate on chest
	3 30 a m	5 0 c c	Intrav Injection over at 3 36 Splotchy rash over chest, abdomen, shoulders at 3 39 Resp 42, reg No wheezes P 144 Occas rhonchus right chest
	3 45 a m		Rhonchi both lung fields Audible resp
	3 53 a m		Adrenalin 1/1000 0 3 c c
	3 55 a m		Blanching of diffuse rash on chest
	3 56 a m		Rhonchi disappeared
	3 57 a m		Rash gone on face
	4 00 a m		Rash on body gone
	4 15 a m		Adrenalin 1/1000 0 2 c c Rhonchi with respirations
	4 22 a m		No rhonchi Lips somewhat cyanotic
	4 47 a m		Intrav Injection over at 8 50
	7 43 a m	7 0 c c	Mottled rash on left arm
	7 56 a m		Wheal over left deltoid, diffuse rash over upper thighs
	7 58 a m		Wheal and rash of left deltoid is blanched
	8 14 a m		
1/8/35	10 55 a m	15 c c	Dr Finland's blood serum intragluteally
	11 00 a m	8 0 c c	Serum intravenous, injection ended 11 07 Blood culture previously taken 11 00 a m T 102° P 140 R 25
			Rough systolic murmur Abdomen more flaccid in epigastrium Still tense in lower abdomen and somewhat distended No rash or rhonchi
1/8/35	3 10 p m	8 0 c c	Intrav T 101.8°, P 140, R 32 Injec over at 3 17
	7 15 p m	8 0 c c	Serum intrav
	7 17 p m		Generalized reddish blush, disappeared in 2 min

Serum Chart—Continued

1/9/35	12 04 a m	60 c c	Serum intrav Injec completed at 12 09 Generalized bluish lasting 1 min and fading No rhonchi
	10 30 a m	80 c c	Serum intrav injected in 4 min Generalized bluish immediately
	10 35 a m		Faded
	10 36 a m		Blotchy rash on hands (palms) present
1/10/35	12 15 p m	80 c c	Serum intrav Injected in 5 minutes
	12 21 p m		Slight flush to face
	12 22 p m		Coughing, no wheezes Wheal 4 cm at site of injection
			Erythema 1 cm about wheal
	12 35 p m		Wheal disappeared
	12 48 p m		Erythema disappeared
1/12/35			Papular red rash around pubis, buttocks and ankles
1/13/35			Macular blotchy rash, itchy, over cheeks, wheals over left upper arm Still coughing Evidents edematous Dis appeared in p m
1/13/35	11 30 a m		Blotchy raised rash on face and outer thighs Wheals and marked itching
Condition			Improved
Diagnosis			Idiopathic pneumococcus Type I peritonitis

The usual leukocytic response in pneumococcic peritonitis resembles more that of an acute septic type of hyperleukocytosis than the moderate elevation found in the ordinary cases of acute appendicitis. Glass²⁰ commented on the frequency with which counts of 30,000 or more are encountered in pneumococcic peritonitis. Gibson²¹ stressed the extraordinarily high leukocyte count with a high percentage of polymorphonuclears as a valuable point in differentiating this type from the appendiceal and non-pneumococcic forms of peritonitis. The white blood cell counts in this case did not conform to Gibson's formula, the highest being 18,400. However, Lazarus²² has noted similar low counts in several patients critically ill with the acute serous type of primary pneumococcic peritonitis.

SUMMARY

Primary pneumococcic peritonitis is a disease occurring chiefly in female children. The mortality rate is very high, both in operated and unoperated cases, especially in the acute serous type of primary pneumococcic peritonitis. A case of this severe type of primary pneumococcic peritonitis with Type I pneumococcic septicemia which responded to the administration of specific serum, is reported. Complete recovery without complications ensued and the patient was discharged in 16 days. In view of the fact that pneumococci reach the blood stream early in the course of this infection, repeated blood cultures are indicated in every patient in the hope of finding a type amenable to specific sero-therapy.

CONCLUSIONS

Early specific sero-therapy in the treatment of primary pneumococcus peritonitis, we believe, offers a non-surgical method of attack, which may prove valuable in selected cases and should be given wider trial.

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THROMBOPENIC PURPURA ASSOCIATED WITH CATARRHAL JAUNDICE REPORT OF A CASE

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A PATIENT has been observed in whom an acute thrombopenic purpura occurred simultaneously with an acute catarrhal jaundice. The case is reported because of its uniqueness † and because of some of the theoretical implications involved.

CASE REPORT

A O, a single, male medical student, aged 24, entered the Passavant Memorial Hospital on November 3, 1934, complaining of malaise, epistaxis and jaundice.

* Received for publication August 17, 1936

From the Department of Medicine Northwestern University Medical School

† No similar case report could be found in the literature

Laboratory Data During Remission of Thrombopenic Purpura and Jaundice

Date Nov 1934	RBC mill per cu mm	Hgb gm per 100 c c	WBC per cu mm	Plate- lets per cu mm	Bleed- ing Time min	Clot Re- traction	Urine		Feces Blood Benzidine Test	Van den Bergh mg per 100 c c	Icterus Index Units	Liver Function
							Blood	Bile				
11-3	5 00	16 0	9950	none	20 +	none	50 cells h p f *	+++				
11-5	5 36	16 0	5500	none	15	none	gross	+++	++++	7 0	90	
11-7				30,000	5		gross		++++			
11-8	5 17	15 6	5500	60,000	3	fair	75 cells h p f	+++	+++	6 7	70	Bromsulphalein (2 mg per kilo) 5 min 90% dye re- tention, 30 min 50% dye retention
11-9							10 cells h p f	++	+++		60	Levulose (50 grams) Hrs 0 $\frac{1}{2}$ 1 2 3 Mg† 77 107 116 104 87
11-12				230,000	2		0	+	0		25	
11-19	4 34	13 4	7000	370,000	2		0	0	0	0 7	20	Bromsulphalein (2 mg per kilo) 5 min 40% dye re- tention, 30 min 10% dye retention

* h p f high power field

† mg reducing substance per 100 cc blood

History The family history and past history were irrelevant. The present illness began October 1, 1934, when the patient contracted an upper respiratory infection. Following this, he felt below par. On October 30, he had loss of appetite, muscular aching, constipation, and discomfort in the abdomen. The next day the urine was highly pigmented, and the stools lighter than normal. The following day (November 1), the patient noticed slight icterus and remained in bed. On November 2, he had nose bleeds, and petechial spots appeared on the trunk. He continued to have light stools and constipation, but the aching and abdominal discomfort subsided. The patient was admitted to the hospital the next evening. No drugs had been taken during this illness.

Physical Examination The physical examination revealed a well nourished, somewhat apprehensive young male who did not appear to be very ill. There was bleeding from the left nostril. The sclerae and skin were moderately icteric. Numerous petechial hemorrhages were present on the lips and gums, and were also scattered all over the body. Subcutaneous hemorrhage was not readily produced by pinching the skin. The heart and lungs were normal. The liver was not palpable, but the tip of the spleen was palpated at the costal margin on deep inspiration. The temperature was 98.8° F, pulse 80, and respiration 20. The blood pressure was 114 mm of Hg systolic, 70 mm diastolic.

Laboratory Examination The significant laboratory data are best presented in tabular form (see table). It is apparent that the laboratory signs were those of thrombopenic purpura with bleeding from the kidneys and the gastrointestinal tract. The direct Van den Bergh test showed a positive prompt and negative delayed reaction, while the indirect quantitative test and icterus index were markedly increased. The bromsulphalein test showed a marked retention of the dye when performed on the fifth day, while the levulose tolerance was practically normal when first studied on the sixth day after admission.

Additional laboratory data not listed in the table revealed the following: Reticulocyte counts on two occasions, less than 1 per cent. Erythrocyte volume index, 106. Fragility test, within normal limits. Differential polymorphonuclear neutrophiles, band forms 0, segmented forms 67 per cent, lymphocytes 21 per cent, monocytes 12 per cent. Coagulation time, 2 minutes. Urine pigmented, contained erythrocytes. Feces dark brown, HgCl₂ test for urobilin and bilirubin negative, benzidine test markedly positive. Blood calcium, 10.9 mg per 100 cc.

On the fourth day after admission, a tube was inserted into the duodenum, and a thin greenish mucoid secretion was obtained after administration of 100 cc of magnesium sulphate. Inoculation of the patient's blood into a guinea pig showed a negative test for Weil's disease.

Course and Treatment No fever or tachycardia occurred at any time during the course of the disease. On the second day after admission (November 5), the patient received a transfusion of 250 cc of citrated blood, and the following day 50 cc of whole blood into the buttocks. Beginning November 5, parenteral liver extract (1 cc derived from 33 1/3 gm liver*) and calcium gluconate and viosterol were given daily. For three days after admission, the petechiae increased, bleeding from the nose became more severe, and there was an increase in bleeding from the kidney and gastrointestinal tract. On November 6, the patient began to improve, and by November 8 all gross bleeding had stopped. Clinical and laboratory signs of the thrombopenic purpura rapidly returned to normal. At the same time, there was continuous improvement in the jaundice. The patient was discharged from the hospital November 24, three weeks after admission, in excellent condition. There has been no recurrence of symptoms up to the present time, one and one-half years after the illness occurred.

* Lederle's Concentrated Liver Extract

COMMENT

The thrombopenic purpura and jaundice in this patient began at about the same time and ran a similar course. The improvement that occurred following the blood transfusion and liver therapy may have been a coincidence. From the clinical picture, the jaundice was apparently of the catarrhal type. Whether actual liver damage occurred or not is uncertain. Many authors^{1, 2, 3, 4, 5} have reported a decreased galactose tolerance in patients with catarrhal jaundice and have usually interpreted this as being evidence of parenchymatous liver disease. In our case, the levulose tolerance curve was practically normal when first studied on the ninth day of the illness. This does not preclude an earlier pathologic curve, as Jolliffe⁶ has shown that the decreased levulose tolerance in catarrhal jaundice may return rapidly to normal shortly after the blood bilirubin reaches its peak.

There are several theories that might explain the etiologic relationship between the thrombopenic purpura and the catarrhal jaundice, namely, (1) they may have occurred independently, (2) they may have been caused by the same etiologic process, and (3) the purpura may have been secondary to the catarrhal jaundice. The latter theory will be considered further, because certain reports in the literature suggest that thrombopenia may be related to liver disease.

The bleeding tendency that often accompanies jaundice and liver disease is not usually of the thrombopenic type. However, exceptions to this rule have been reported. Loeper and DeSeze⁷ observed a patient in whom purpura occurred along with metastatic carcinoma of the liver. The patient had numerous petechiae, a prolonged bleeding time, a normal coagulation time, and a delayed clot retraction. The platelet count was not reported. Willebrand⁸ described three cases in which thrombopenic purpura was associated with liver disease. Two of his patients had metastatic carcinoma of the liver, and a third had an acute yellow atrophy of the liver following salvarsan therapy. Recently, Abram⁹ discussed this subject under the title of hepatic purpura. He described two cases, one of atrophic cirrhosis and another of spleno-hepatic disease of syphilitic origin. Both patients had purpura, a prolonged bleeding time, a positive tourniquet test, and non-retraction of the clotted blood. The platelet count was not reported in the first case, but was 82,000 per cu mm in the second. Splenectomy was specific in controlling the hemorrhagic tendency in both cases. Abram believes that true purpura in liver disease is due to involvement of the "spleno-reticulo-endothelial" system and is not due to the liver insufficiency per se.

Very few data on the platelet count in liver disease are available in standard reference books. Jones and Minot¹⁰ estimated the number of platelets on blood films from patients with catarrhal jaundice and found them to be within normal limits. During recovery from the disease, there was an increase in the thrombocytes. Weil et al¹¹ reported a diminution in platelets in 18 out of 20 patients with liver lesions. Their series consisted mainly of cases of cirrhosis and chronic congestion of the liver. King¹² found a thrombopenia in 20 per cent of patients with portal cirrhosis of the liver. Fellingner and Klima,¹³ studying a group of patients with cirrhosis of the liver, frequently found a decrease in platelets which was related to the degree of liver involvement. In one advanced case, the platelet count was 20,000 per cu mm, the bleeding time was

prolonged, and the clotting time was normal. The thrombocyte level is said to be low in acute yellow atrophy of the liver^{14, 15}. Higgins and Stasney¹⁶ reported a decrease in platelets to one-third of normal in rats with cirrhosis of the liver produced with carbon tetrachloride. A diminution in the leukocytes or erythrocytes may also be associated with hepatic disease. Leukopenia is reported to occur in catarrhal jaundice¹⁷ and cirrhosis of the liver,^{12, 18} while anemia is frequently associated with various types of liver disease¹⁹.

The cause of the decrease in thrombocytes in liver disease is not apparent. As Abram⁹ has suggested, the decrease might well be related to an associated pathologic process in the spleen rather than to the liver condition itself. The influence of the spleen on the blood platelets is evident in such diseases as thrombopenic purpura and splenic anemia where splenectomy is followed by thrombocytosis. Another possible mechanism in the pathogenesis of the thrombopenia in liver disease might be through the deficiency of a nutritional factor necessary for thrombopoiesis. For example, the macrocytic anemia of advanced cirrhosis is thought to result from the inability of the liver to store a necessary hemopoietic principle¹⁹.

From the evidence presented, it seems possible that the thrombopenic purpura in the patient reported could have been secondary to the catarrhal jaundice. A case of this type is a stimulus to further clinical and experimental observations.

SUMMARY

1. A case is reported in which thrombopenic purpura occurred simultaneously with catarrhal jaundice.

2. Evidence is presented which suggests a relationship between thrombopenia and liver disease.

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CHLOROMA, REPORT OF A CASE¹

By HAROLD R ROEHM, M D, F A C P, AARON RIKER, A B, M D, and
RICHARD E OLSEN, Sc D, M D, *Birmingham, Michigan*

CHLOROMA is not a common form of malignant tumor Washburn¹ in a review of the literature through June 1929 found 162 cases Since that time 32 more have been reported, bringing the total to 194

Dock and Warthin² in 1904 published an exhaustive study of the clinical and histological features of the disease Their conclusion was that, "chloroma is a tumor-like hyperplasia of the parent cells of the leukocytes, primarily in red marrow, the periosteum being secondarily involved"

In the past, opinions have been divided concerning the lymphatic or myelogenous origin of the neoplasm, but the general opinion at present would indicate that the majority of chloromas are myelogenous in origin

The prognosis of patients with chloroma has been universally bad with two exceptions The first, reported by Lecène,³ was a case of a tumor of the humerus, which was treated by amputation and roentgen-ray therapy, the second, reported by Washburn,¹ was a case of tumor of the left frontal bone of the skull, with operative removal and subsequent roentgen-ray therapy Swanson,⁴ Rosenblum,⁵ Doub and Hartman,⁶ and others failed to find roentgen therapy to be of value in influencing the final outcome of the disease

We believe the following case of chloroma cannot be classified as either lymphatic or myelogenous in origin as the tumor cell is a primitive blast which might conceivably differentiate into either a lymphocyte or a myelocyte

CASE REPORT

Elizabeth S, white female, aged 13 years, was brought to the hospital February 21, 1936, because of weakness, anemia, and vomiting She had been irrational for the preceding 24 hours

* Received for publication August 7, 1936



FIG 1 No 1 Chloroma Neoplastic cells in a lymph node (× 2070)
No 2 Endothelial phagocytes and tumor cells in the dura mater (× 2070)

In November 1935, the patient noticed swelling of the upper eyelids, severe enough at times to tightly close them. She rapidly became weak and pale. She complained of pain referred to the navel and vomiting. In December 1935, the vomiting grew worse, again accompanied by umbilical pain. In January 1936, her right eyelids suddenly became black and this was followed by the same phenomenon in the left eyelids a few days later.

January 10, she was taken to a hospital where she was diagnosed as suffering from malformations of both kidneys. She was given two blood transfusions with only transient benefit. Frequent nasal hemorrhages began. No bowel movements could be obtained. She was discharged January 25, slightly improved.

On February 12, 1936, persistent vomiting began and continued to the time of admission (February 21). There was a familial history of cancer.

Physical examination. The patient was extremely anemic and emaciated, irrational, and apparently almost deaf. She appeared to be nearly blind. The upper eyelids showed moderately firm swelling with dilated superficial veins. There was no exophthalmos. Crusts of dried blood were present in both external nares. The cervical, axillary, and inguinal glands were all palpable, discrete, and bean sized. There was an apical systolic cardiac murmur probably due to the anemia and not organic in origin. Examination of the chest revealed no evidence of disease. The abdomen was scaphoid with almost no panniculus. Tenderness was present in both upper quadrants but particularly the right. A smooth mass occupied the upper right quadrant from the ribs down to the level of the umbilicus. This mass was flat to percussion and poorly defined in outline, and appeared to be a greatly enlarged liver. The remainder of the examination was essentially negative.

Laboratory examinations. Ten consecutive urine analyses showed positive albumin, a trace of sugar, and fields full of granular casts and white and red blood cells. The specific gravity was fixed at 1.010. A blood count (February 21) showed hemoglobin 32 per cent (Dare), red blood cells 650,000 and white blood cells 10,100 per cu mm, polymorphonuclear neutrophils 47 per cent, lymphocytes 48 per cent, monocytes 5 per cent. Nothing abnormal was noted about any of the white blood cells. The sedimentation rate of the red blood cells was 44 mm in 60 minutes (Cutler). Blood non-protein nitrogen was 28.5 mg per 100 cubic centimeters. The stools contained four plus occult blood. The blood Kahn was negative.

Eye examination (February 27) revealed the following. The pupils reacted sluggishly to light and accommodation. They were dilated under homatropine and cocaine. No protrusion, nystagmus or paralysis of either eyeball was noted. The anterior and posterior chambers and lens were clear. Both eyes showed marked vitreous opacities. The fundus examination of the right eye showed over four diopters choking of the disc, with the vessels of the retina engorged and tortuous. There were marked masses of hemorrhage throughout the retina with small white areas noted in the center of the masses. The largest mass of hemorrhage was in the superior temporal portion of the fundus. A definite cherry-red spot showed around the fovea. The fundus examination of the left eye showed the same characteristics, except that the largest mass of hemorrhage was found posterior and towards the temporal side. A cherry-red spot also showed around the fovea and about two diopters choking of the disc was noted.

Roentgen-ray examination by Dr. J. E. Church (February 22, 1936) showed that the left lung field was a trifle more radiolucent than the right although no definite pathologic changes could be defined. An attempt was made to examine the upper gastrointestinal tract but the patient was non-cooperative and only a minute amount of barium was taken. A single anterior-posterior film was taken showing some of the meal had passed into the small intestine, which suggested that there was no obstruction of the pylorus. Some flakes of barium or bismuth which were found in

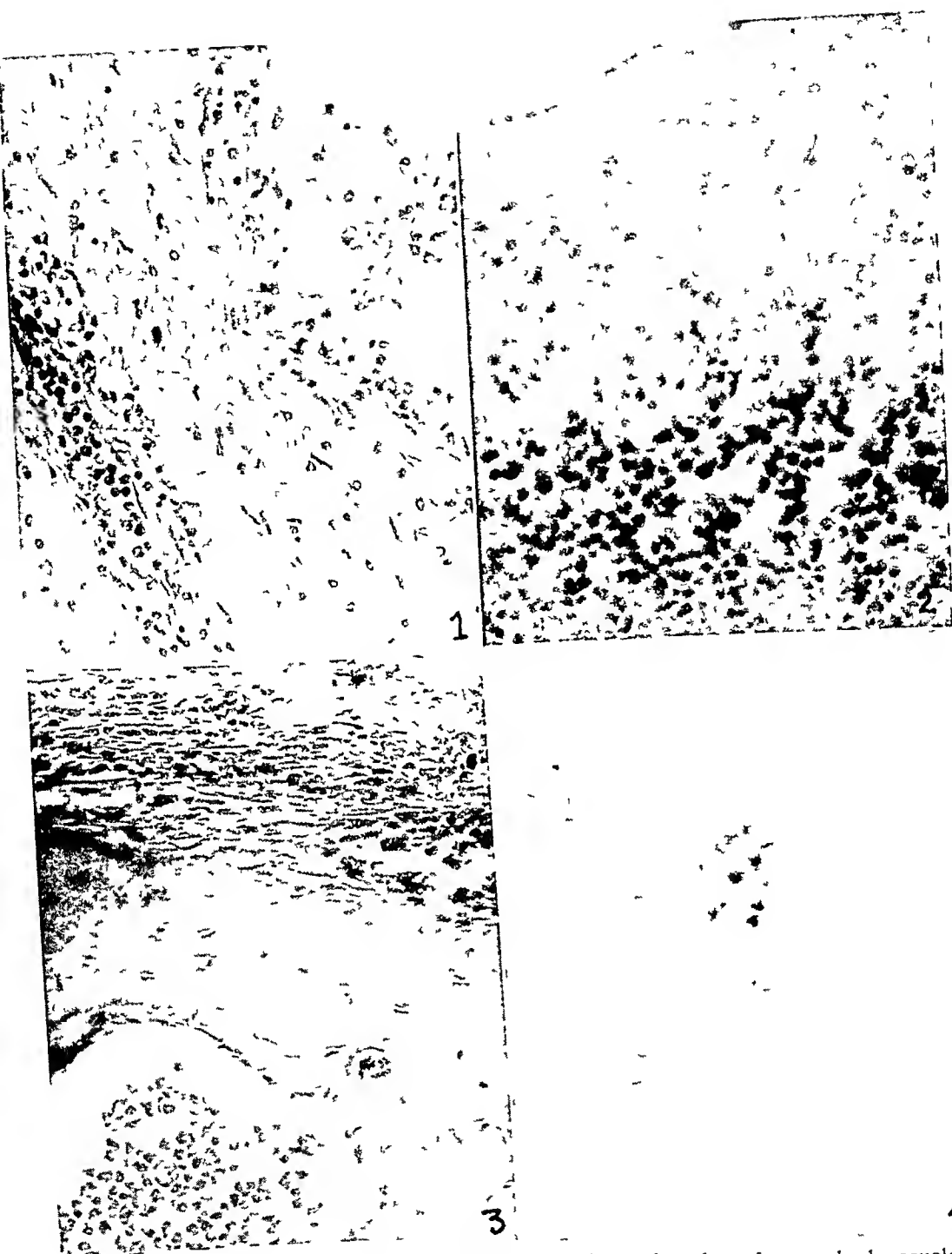


FIG 2 No 1 Arteriole filled with tumor cells at the edge of a cerebral vacuole ($\times 230$)
 No 2 Tumor cell invasion of the dura mater ($\times 230$)
 No 3 Pleural surface of a rib showing the tumor cell infiltration of the periosteum and marrow ($\times 230$)
 No 4 Peroxidase granules present in a polynuclear leukocyte but absent in the tumor cells ($\times 2070$)

the region of the rectum were due to some former examination or medication. The left kidney was not outlined, but the right was well defined, appearing as if it might be a little larger than normal.

A provisional diagnosis of lymphosarcoma with metastases to the brain was made as a result of the examinations.

Course of the disease. Twenty-four hours after admission the patient was given a transfusion of 500 cubic centimeters of whole blood with some transient improvement. The temperature ran an irregular course from 100° to 104° F. Five hundred cubic centimeters of 5 per cent glucose in normal saline were given twice daily. This was useful in controlling the persistent vomiting. Frequent hemorrhages from the nose occurred daily. The patient rapidly failed in spite of supportive treatment and expired March 1, 1936, nine days after admission.

Autopsy report. The autopsy was done one and one-half hours after death. External examination showed a female at the age of puberty who was markedly emaciated and very pale. There was moderately firm swelling of the upper eyelids.

Internal examination revealed about two liters of clear yellow fluid in the abdominal cavity. The liver and spleen were much enlarged. The mammary gland tissue was a bright olive green bilaterally. The costal cartilages cut with difficulty. The periosteum on the internal surface of the sternum and ribs was thickened and was almost uniformly bright green and the thymic fat in the anterior mediastinum was of the same color. About one liter of orange colored fluid was present in each pleural cavity and 100 cubic centimeters in the pericardial sac. There was one green spot on the anterior surface of the pericardial sac. The heart blood clots were maroon. No green areas were seen in the myocardium. The gross cardiac lesions were limited to a rather marked sclerosis of the aortic ring, involving the orifices of the coronary arteries. The lungs were bizarre in appearance having many reddish-purple and a few green slightly elevated areas over the surfaces of both lungs, the largest of these was not more than two centimeters in diameter. The peribronchial lymph nodes were uniformly olive green in color and varied in size up to one centimeter in diameter. The lungs were nodular on palpation, the nodules being the discolored areas described. On the cut surface there was revealed a bilateral bronchial pneumonia.

The liver measured 25 by 24 by 8.5 centimeters and was a maroon color. On the cut surface no gross tumor nodules were found and the liver lobules were distinctly outlined. The spleen measured 16.5 by 9 by 4.5 centimeters. The capsule was purple and tense. On the cut surface there were greenish spots scattered at intervals, none of them being over one-half centimeter in their greatest diameter. The peri-esophageal lymph nodes were green but the remainder of the gastrointestinal tract showed no green areas, and the mesenteric nodes though enlarged up to a maximum of 3 centimeters in size were maroon in color. The stomach showed petechial hemorrhages. The retroperitoneal lymph nodes were 2 centimeters in length and were olive green. The periaortic nodes had the same appearance.

The kidneys were studded with subcapsular green nodules up to 1 centimeter in diameter. The adrenals were small but showed no discolorations. The uterus showed several greenish nodules on the serosal surface, and the endometrium was olive green. The ovaries showed no gross pathologic change. The vertebral bodies had some greenish spots on their anterior surfaces and were unusually soft so that they could be cut easily with a knife. The ribs were almost as soft as the costal cartilages, and their bone marrow varied from maroon to olive green. The bone marrow of the sternum was maroon.

The periosteum of the skull was green near the midline, and was slightly thickened. The bones of the skull were harder than the ribs and vertebral bodies but still were softer than normal and their bone marrow was brown. The dura mater was thickened to one-half centimeter near the midline and was olive green. The

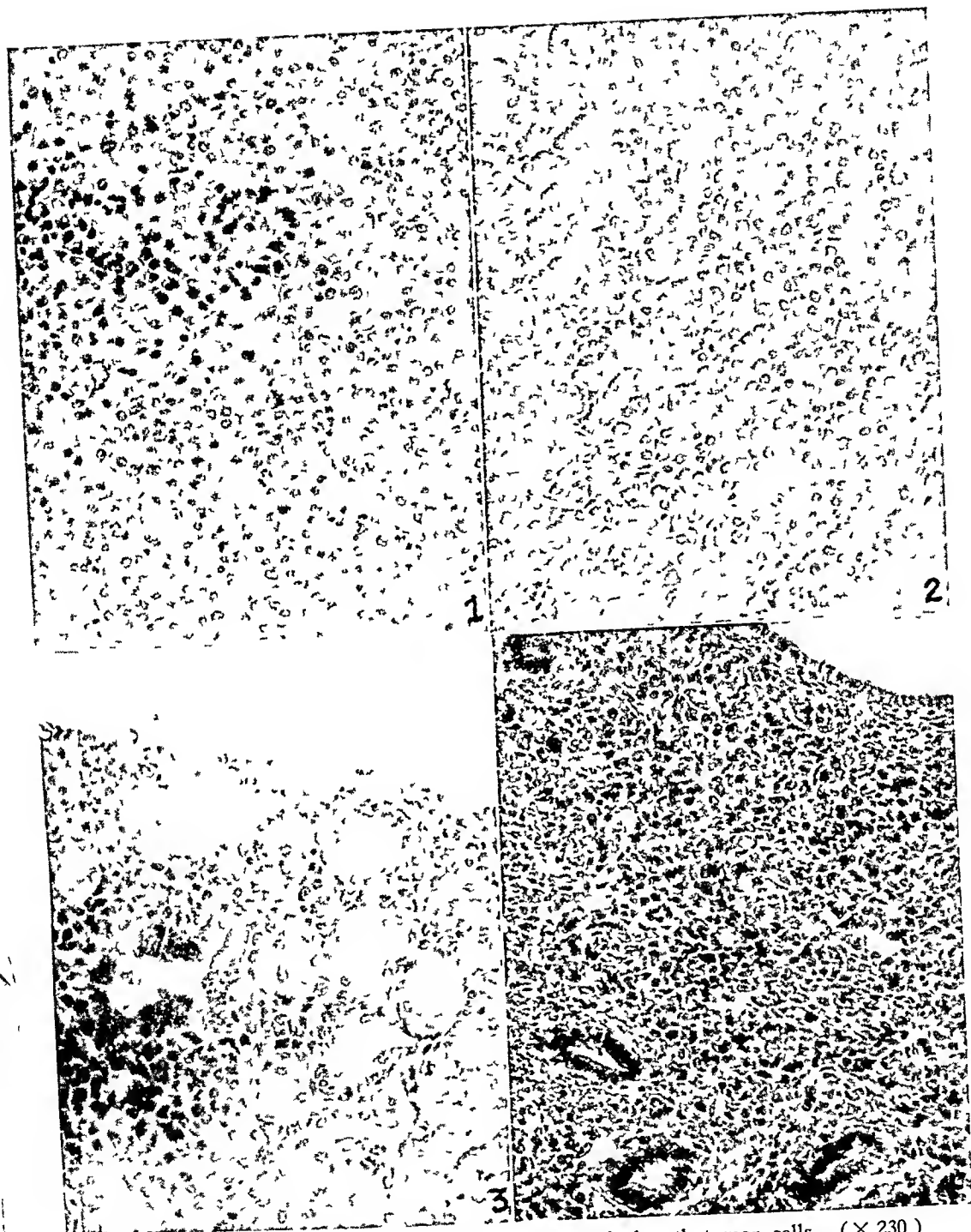


FIG 3 No 1 Blood capillaries of the liver packed with tumor cells ($\times 230$)
 No 2 Neoplastic invasion of a pancreatic lobule ($\times 230$)
 No 3 Edge of a tumor cell nodule in the renal cortex ($\times 230$)
 No 4 Uterine endometrium heavily infiltrated by tumor cells ($\times 230$)

spinal fluid was clear and showed no increase in pressure. The cerebrum was moderately edematous and on the cut surface showed multiple cystic spaces up to one centimeter in diameter. These contained a cloudy yellow fluid. The only green area found in the brain was in the choroid plexus of the left lateral ventricle.

The pituitary was replaced by a mass of green tumor tissue which measured 2.4 by 2.3 by 1.3 centimeters. The sphenoidal sinus and posterior ethmoidal air cells were filled with the tumor tissue. Both orbital cavities were invaded in the retro-orbital recesses by tumor tissue with partial destruction of the supra-orbital plates. The retropharyngeal canal was patent and a probe could be readily passed from the much enlarged sella to the pharyngeal mucosa.

On microscopic examination the tumor tissue was found to have a very wide distribution corresponding to the green and maroon areas described grossly. The tumor cell was a round or oval cell averaging from nine to twelve microns in diameter in the section. The nucleus was placed acentrically at the edge of the cell and showed a rather lightly staining chromatin material without radial distribution of the granules. The cytoplasm was quite plentiful and was clear. No eosinophilic or basophilic granules were present. The cells were constant in their appearance in all tissues. Eosinophilic and neutrophilic polynuclear cells were quite numerous. There were many pigment laden phagocytes present, especially in sections from the nodules which grossly had shown a green color. This pigment was phagocytized blood from obstructed capillaries and varied from recognizable red blood cells through amorphous masses to crystalline deposits.

The various tissues retained in part their specific structures but showed a diffuse or massive infiltration of tumor cells. The lymph nodes and spleen were extensively infiltrated by tumor cells but the lymph follicles persisted to some extent. The liver cells were atrophic due to the tumor cell invasion and anoxemia. The blood vessels throughout the body were filled with tumor cells indicating that a marked leukemia was present at the time of death.

The vacuoles found grossly in the brain showed few tumor cells about them and represented a simple liquefaction process. This necrosis was produced by the obstruction of many of the arterioles by tumor cells with resultant small localized anemic infarctions of the cerebral substance. The pituitary was almost completely destroyed by tumor tissue and it was only with difficulty that any trace of its original structure could be found. The pancreas in addition to small masses of tumor cells showed areas of endothelial phagocytes having a foamy appearance.

Autopsy summary. A chloroma was found involving the periosteum of the skull, ribs, sternum, and vertebral bodies (the long bones were not examined), the thoracic and abdominal lymphoid tissue, the thymus, lungs, pericardial sac, liver, spleen, pancreas, kidneys, dura, pituitary and choroid plexus of the left lateral ventricle. The tumor was in a leukemic phase with all the vessels showing an abundance of the tumor cells. There was marked anemia and a generalized edema with pitting of the ankles and feet, a fatty degeneration of the liver and kidneys, calcification of the costal cartilages with abnormal softening of the bone of the ribs, sternum, vertebral bodies, and to a lesser extent of the skull cap. The cerebral arterioles were thrombosed by tumor cells with multiple areas of liquefaction necrosis. The thyroid gland and adrenals were hypoplastic. There was a terminal bronchial pneumonia.

DISCUSSION

Nine days before death the patient had a white blood count of 10,100 white blood cells with no recognizable cancer cells in the blood stream. At autopsy there was a marked leukemia, sufficient to cause thrombosis of the cerebral vessels. The examination of the eyes three days before death showed definite evidence of leukemia with thrombosis of the arterioles.

The complete destruction of the pituitary might well have been related to the calcium deficiency in the bones and increase in the cartilages. No roentgen-ray evidence of such a change was noted during the examination eight days before death.

Fixed sections of the tumor stained with Weigert's iron hematoxylin and eosin, Goodpasture's oxidase stain and Wright's stain were examined by Dr Raphael Isaacs of the Simpson Memorial Institute at Ann Arbor and Dr Carl V. Weller of the University of Michigan. Dr Isaacs concluded that the tumor cell, which in no case showed oxidase granules, was of the lymphocytic series rather than of the myelocytic series, but might possibly be of the plasma cell type. Dr Weller felt that no classification of the cell as to lymphocytic or myelocytic origin was justifiable and that the tumor cell was too primitive to indicate the potentialities of differentiation of its parent type.

The extensive deposits of blood pigment in various stages of phagocytization in the tumor nodules were responsible for the green discoloration of tissue which characterized the so-called chloroma. There was no evidence in our case that the tumor cells themselves had any relationship to the green pigmentation. There may have been a faulty production of hemoglobin or an increased destruction—which, we are not prepared to say—but the green color was due to phagocytosis of the red blood cells in the capillaries in the tumor nodules. Tumor nodules may uncommonly occur without any green color, and in the leukemic invasion of the organs there is no green pigmentation.

It is to be noted that the tumor affecting bone appeared upon only one side in every case, that side being the one where the nutrient vessels entered the bone.

SUMMARY

A case is reported of chloroma in a 13 year old white female. The tumor was in an aleukemic phase nine days before death but was leukemic at death. There was a very extensive involvement of the cranium and body viscera. The tumor cell did not show the oxidase reaction.

CONCLUSION

- 1 Chloroma is a faulty designation as the green coloration is not specific of any one tumor cell type.
- 2 The green pigmentation is due to phagocytosis of the blood in the obstructed capillaries by the endothelial cells.
- 3 The tumor cell of chloroma is not necessarily myelocytic in origin.

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EDITORIAL

THE REPORTED INCREASE IN INSANITY AND FEEBLEMINDEDNESS

It has been frequently stated that an alarming increase is occurring in the numbers of the insane and of the feeble-minded. This assumption has influenced many legislators in favor of optional or compulsory sterilization of the mentally afflicted as a means of limiting this increase. In May of 1934 the American Neurological Society appointed a committee to study the whole question of eugenical sterilization. This committee, working under a grant from the Carnegie Foundation, brought in its preliminary report in 1935. The full report has only recently been available in published form.¹ It contains a very interesting review of the data bearing upon this matter of the increasing frequency of insanity and feeble-mindedness.

In previous studies great stress has been laid upon the rapid rise in the number of insane per 100,000 of population as indicating a great increase in mental disease. There exists, however, no adequate survey of the entire population and the rates quoted are based for the most part upon the number of hospitalized insane in the community. This number, however, can not be taken as a true index of the incidence of mental disease since it is very obviously influenced by the growing recognition on the part of the public of the desirability of commitment, by prevailing economic situations which may render commitment as opposed to the expense of home care more imperative, and by the availability of adequately equipped hospitals which diminishes the family resistance to institutional care for one of its members. The number of hospitalized insane no doubt bears some relation, modified by the above factors, to the total of living cases in the population, but a much less definite relation to fluctuations in incidence. A study of various states shows that where the level of public education is high and where well-managed psychopathic institutions are provided the commitment rate is high whereas in states with a lower level of literacy and with few and poorly equipped mental hospitals the commitment rate is low.

It has been argued that the stress and strain of city life are potent factors in producing insanity, and the higher percentage of urban cases confined in institutions has been cited in support of this view. The explanation however, may be that the residents of cities are better informed as to the value of psychiatric care, that the necessary institutions are usually nearer at hand and that the home care of the insane is less feasible in crowded city living quarters than on farms.

¹ Eugenical Sterilization, Committee of the American Neurological Association for the Investigation of Eugenical Sterilization. New York, The Macmillan Company, 1936, page 211.

The committee made a special study of two relatively stable communities, the states of New York and Massachusetts, to see whether new data representing more accurately the fluctuations in true incidence of mental disease could be obtained. In both of these states there has been a well publicized campaign for mental hygiene for some years, and both are well provided with strategically placed mental hospitals. It was felt that a study of the admission rate (first admissions), as opposed to the number of inmates of hospitals, in these two states over a period of years might throw new light on the subject.

In the interpretation of the data the estimated increase in the population has been taken into account as well as the fact that the average age of the population is increasing. Also the age periods at which the various psychoses occur has been allowed for. Since paresis, for example, rarely occurs in those under thirty-five, the admission rate of paretics was calculated in relation to the quota of the population thirty-five or over. The lower age limit for manic depressive psychosis and for dementia precox was taken as fifteen, that for cerebral arteriosclerotic and senile dementias as fifty-five, and that for all psychoses combined as fifteen years. In Massachusetts the period studied was from 1920 to 1933, both inclusive, and in New York the years 1917 to 1934, both inclusive, were reviewed.

In Massachusetts the admission rate for all psychoses combined was 102.0 per 100,000 in 1920. In the ensuing years it fell as low as 94.0 and rose as high as 118.0 but for the last three years of the period studied the figures were 100.0, 98.5 and 102.0. Similar figures for all psychoses in the state of New York were 94.9 in 1917 and for the last three years of the period 106.0, 110.0 and 111.0. It is apparent that there has been at least no alarming increase in the admission rate for mental disease in these two large and relatively stable communities in the period investigated.

The analysis of the various groups of mental disorders as to their admission rates revealed some interesting facts. The combined group of manic depressive psychosis and dementia precox showed no significant change in admission rate during the period involved. The alcoholic psychoses in New York State showed a marked drop in admission rate during the first few years before and after prohibition was instituted, but thereafter the rate rose gradually to preprohibition levels. The admission rate of paretics showed a definite fall in both states. In New York State there was a definite and probably significant increase in the admission rate for cerebral arteriosclerotic and senile dementias.

The investigations of Winston² have shown that admission rates to mental hospitals, corrected for age, have shown no tendency to rise in recent years in England, Wales, Scotland, Australia, New Zealand or the Scandinavian countries. A definite increase was noted only in Germany.

² WINSTON, ELLFN. The assumed increase of mental disease, *American Journal of Sociology*, 1935, 41, No. 4.

Such data are of course not conclusive proof that insanity and feeble-mindedness are not increasing. Nothing but repeated surveys of the total population could be considered final. However the results of these studies are much stronger evidence against any great increase than has heretofore been put forward as indicating it.

The conclusion of the committee of the American Neurological Society on this point is of interest. "We do not believe that society needs to hurry into a program based on fear and propaganda. Although the problem of mental disease and defectives is enormous, there exists no new social or biological emergency."

REVIEWS

Modern Treatment and Formulary By EDWARD A. MULLEN, P.D., M.D., F.A.C.S., Assistant Professor of Pharmacology and Physiology, Philadelphia College of Pharmacy and Science, Lieutenant Commander Medical Corps, U.S. Naval Reserve. 707 pages, 20 × 12 cm. F.A. Davis Company, Philadelphia. 1936. Price, \$5.00.

This concise treatise on treatment is designed to be of ready use to the practitioner in his daily office and bedside work. The major portion of the volume is devoted to the materials of pharmacotherapy. The presentation of the physician's drug armamentarium is set forth in more than two thousand suggested prescriptions. The latest Pharmacopoeial nomenclature is employed. The arrangement of the *materia medica* is under the names of the diseases, cross references are frequent.

The appendix of the book considers many subjects in resume form of special interest to the physician. Among these subjects are formulae for fluid foods, diet tables, intravenous technic, dose tables and the antidotal treatment of various poisons.

The reviewer regrets that the table of antidotes is fragmentary. Doses of antidotes and specific information are not frequently included. The established nitrite-thiosulfate treatment of cyanide poisoning is omitted, most unfortunately the sodium formaldehydesulfoxylate treatment for bichloride of mercury poisoning has not been included and the treatment for barbiturate poisoning is naive and insufficient.

In the light of modern pharmacological opinion, i.e., writing a prescription based on the known action of one dependable drug, many of the prescriptions included seem archaic and bear the markings of the age of polypharmacy. Thus in one prescription, page 202, for enuresis the drugs *rhhus glabra*, ergot, belladonna, *triticum* and *jaborandi* are prescribed.

Despite the above criticisms the author is to be congratulated on the compilation in such readily accessible manner of so much useful information pertinent to the daily work of the practitioner.

J. C. K., JR.

A Text-Book of Pharmacology and Therapeutics or the Action of Drugs in Health and Disease By ARTHUR CUSHNY, M.A., M.D., LL.D., F.R.S. Eleventh Edition, thoroughly revised by C. W. EDMUNDS, A.B., M.D., Professor of *Materia Medica* and Therapeutics and Director of the Pharmacological Laboratories, University of Michigan, and J. A. GUNN, M.A., M.D., D.Sc., F.R.C.P., Professor of Pharmacology and Director of the Nuffield Institute for Medical Research, University of Oxford, England. 808 pages, 23 × 15 cm. Lea and Febiger, Philadelphia. 1936. Price, \$6.50.

Pharmacologists welcome again the revision of this widely used treatise on the action of drugs. Eleven revisions bespeak its usefulness in the fields of pharmacology and medicine. Although three years only have passed since the appearance of the last revision of this text, the rapid strides in the field of medication embraced by the new volume make its appearance timely.

The book is divided into an introduction and seven parts. Part I includes the action of inorganic substances, Part II embraces substances which are characterized chiefly by their local action, in Part III, the action of drugs after absorption is discussed, Part IV treats of anthelmintics, Part V is devoted to antiseptics and disinfectants, Part VI is concerned mainly with *Chaulmoogra* oil and the subjects of Part VII are vaccines, toxins and antitoxins.

With certain slight alterations the arrangement of the contents has not been changed greatly. Simpler substances, e.g. salts, have been placed nearer the front of the treatise and groups of drugs have been collected into larger classes.

Many of the subjects which were missing in the last edition are to be found in the present revision. Among these is a short resume of the action of drugs on cells, an extension of the sections on liver therapy, arsphenamine, avertin, atabrine and carbarsone.

The modern treatment of cyanide and mercuric chloride poisoning is included, though the mechanism of the action of the latter is not mentioned. The statement on page 428 that picrotoxin has not been employed in therapeutics in cases of collapse is questionable.

The style of the book is concise and lucid and its general printing, arrangement, excepting many of the structural formulas, is excellent.

The reviewer is of the opinion that this revision, like those in the past will continue to rank high among the textbooks in the English language.

J C K, JR

Chronic Indigestion By C J TIDMARSH, M A, M D, F R C P (C) 143 pages
14 X 20 cm Longmans, Green and Company, New York 1936 Price, \$1 50

The author's purpose in writing the book apparently seems to be threefold. He desires to educate the patient, to supplement the advice of the physician and to stress the need for cooperation between patient and physician. The information given is not intended to allow the patient to treat himself but rather to help him in carrying out instructions intelligently.

The book is written in elementary style and does not go over the heads of its lay audience. The approach through anatomy and physiology to causes, symptoms, diagnosis (investigation of case) and treatment gives the layman the accepted method of understanding disease processes. The limitation of its discussion to the type of indigestion associated with definite pain accounts for the author's ability to keep the size of his book within commendable limits.

It is indeed gratifying to see the emphatic indictment of the use of tobacco as an accessory factor in the production of peptic ulcer. It would seem, however, that other dogmatic statements are out of place in a book of this kind. Reference is made to such remarks as "ulcer pain is never present before breakfast" and "vomiting never occurs in the absence of pain." Moreover, in the discussion of cancer of the stomach the mere mention that "a person over 35 years of age who has not had previous attacks of indigestion and now complains of loss of appetite, etc., should be presumed to have cancer of the stomach until proved otherwise," may be enough to cause hysteria. It would be far more desirable in writing for laymen to suggest that such may be a possibility. The remarks about healing of ulcer are also somewhat misleading. One gets the impression that ulcers heal rather promptly (three to four weeks) whereas in the majority of cases, even under the best of conditions, actual healing is not consummated for months. Patients may as well know this and be resigned to months of cooperation in following out their treatment. The recommendation of sanatoria for ulcer cases is unusual though it may help to impress the patient with the necessity for readjustment of his habits and environment. The stress laid upon complete examination is commendable.

There are other minor criticisms but on the whole the author accomplishes his purpose. The book is concise and proves to be very readable.

S M

Keeping Your Child Normal By BERNARD SACHS, M D 148 pages, 13 5 × 19 cm
Paul B Hoeber, Inc, New York 1936 Price, \$1 50

Out of many years of experience in dealing with the problems of childhood, Dr Sachs has written this little book of mellow wisdom. It is the sort of book that should be read by every physician and layman who has to deal with children—and preferably read in the evening with a leisurely and thoughtful mind. By the same token it will probably be read by very few of the persons most in need of it, because it contains little that is spectacular, and because it offers no new theories to try out on the next little victim who comes along.

Throughout all the pages of his book, Dr Sachs preaches the doctrine of common sense in handling children, and he repeatedly warns against a too eager acceptance of the latest psychological theories of child training. "A little respect for tradition and for the experience of the past is no obstacle to true progress." He shows vividly the harm that may be done to a perfectly normal child by subjecting him, for example, to the influence of a sexually minded psychoanalyst, or the damage done by "modern parents" who subscribe to the doctrine of "complete self-expression" for their youngsters.

Dr Sachs misses very few of the many aspects of child psychology, and there are few that he does not enlighten with a pertinent comment. A multitude of topics such as the responsibility of the father in the guiding of his children, the value of discipline in the very young, the effects of reading and movies, juvenile delinquency, the relative importance of heredity versus environment, the need of inculcating the old-fashioned virtues of consideration, honesty, and industry, the proper conduct of social service agencies and child guidance clinics are all touched on in this book.

The large section of the book, which is devoted to what the author terms "The Use and Abuses of Psychoanalysis," is essentially a biting criticism of psychoanalysis as it is practiced today. This chapter is well worth reading as the opinion of a sane and experienced psychiatrist on this particular subject, but the reviewer cannot see how it contributes very much to the discussion on "Keeping Your Child Normal."

C H

Tuberculosis in the Child and the Adult By FRANCIS MARION POTTENGER, A M, M D, LL D, F A C P 611 pages, 16 × 23 5 cm C V Mosby Company, St Louis 1934 Price, \$8 50

The author's wide experience and uncommonly sane clinical judgment have enabled him to produce a very valuable volume on tuberculosis in the child and in the adult. The modern concepts of the development of primary tuberculosis and of its later course have been fully presented. The subject of the relationships between allergy and resistance in tuberculosis is interestingly discussed. The author feels that allergy plays a large role in combating the infection. The visceral reflexes involved in the symptomatology of pulmonary disease receive full attention. Dr Pottenger has long had a special interest in this subject. He is also among those who attribute considerable therapeutic value to tuberculin. In discussing the diagnostic use of tuberculin more might have been added as to the dangers of the subcutaneous test, and the advantages of the intracutaneous method might have been more strongly set forth. The discussions of the clinical aspects of the disease and of its treatment are excellent. The volume is richly illustrated with roentgenograms. Dr Pottenger's book will be of great value to internists and pediatricians who feel the need of a modern one volume text on tuberculosis.

A H F

COLLEGE NEWS NOTES

LIFE MEMBER

Dr W E Kendall of Oak Park, Ill , has become a Life Member of the College under date of December 14, 1936

GIFTS TO THE COLLEGE LIBRARY

The College gratefully acknowledges receipt of the following gifts to the College Library of publications by its members

Books

- Dr Lawrason Brown (Fellow), Saranac Lake, N Y—one autographed copy, "Rules for Recovery from Tuberculosis",
Dr Walter Freeman (Fellow), Washington, D C—one autographed copy, "Neuropathology The Anatomical Foundation of Nervous Diseases",
Dr Solomon Katzenelbogen (Fellow), Baltimore, Md—one autographed copy, "The Cerebrospinal Fluid and Its Relation to the Blood",
Dr William C Menninger (Fellow), Topeka, Kan—one autographed copy, "Juvenile Paresis",
Dr Anthony C Cipollaro (Associate), New York, N Y—one autographed copy, "Skin Diseases in Children"

Reprints

- Dr Oscar W Bethea (Fellow), New Orleans, La—12 reprints,
Dr Milton A Bridges (Fellow), New York, N Y—3 reprints,
Dr A Allen Goldbloom (Fellow), New York, N Y—2 reprints,
Dr H Beckett Lang (Fellow), Brentwood, N Y—1 reprint,
Dr John W Shuman (Fellow), Los Angeles, Calif—1 reprint,
Dr Virgil E Simpson (Fellow), Louisville, Ky—1 reprint,
Dr Walter C Swann (Fellow), Huntington, W Va—1 reprint,
Dr Hyman I Goldstein (Associate), Camden, N J—1 reprint
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Dr Charles H Cocke (Fellow), Asheville, N C, was the orator for the annual meeting of the Jefferson County (Ky) Medical Society, held during December in conjunction with and sponsored by the Louisville Tuberculosis Association

Dr Edgar F Kiser (Fellow), Indianapolis, Ind , has been elected President of the Indianapolis Medical Society

At the annual meeting of the Rensselaer County (N Y) Medical Society, Dr Stephen H Curtis (Fellow), Troy, was elected President for 1937

Dr Harold Swanberg (Fellow), Quincy, Ill , was reelected Secretary-Treasurer of the Mississippi Valley Medical Society at its annual meeting in Quincy, Ill , during

November Dr Dan G Stine (Fellow), Columbia, Mo , was elected to the Board of Directors for a two-year term for Missouri

The Medical Association of Puerto Rico held its annual meeting in Santurce, P R, December 18-20 Dr O Costa Mandry (Fellow) was President of the Committee on Arrangements A paper on "Applied Therapeutics" by Dr A C Morgan (Fellow), Philadelphia, was read by invitation Other members contributing to the program were Dr Ramon M Suarez (Fellow), "Comparative Effects of Crude and Purified Liver Extracts in the Anemia of Sprue Administered Intramuscularly and Intrasternally", Dr Enrique Koppisch (Associate), "Tissue Reactions in Diseases Caused by Filterable Viruses", and Dr Rafael Rodriguez Molina (Fellow), "Hematological Studies on Malaria in Puerto Rico"

Major General M W Ireland (Fellow) is President of the National Board of Medical Examiners of the United States Among Fellows of the College who are members of this Board are Dr Walter L Bierring, Des Moines, Dr Charles A Elliott, Chicago, Dr Reginald Fitz, Boston, Dr Waller S Leathers, Nashville, Tenn, Dr George W McCoy, U S Public Health Service, Dr William deB MacNider, Chapel Hill, N C, Dr Walter W Palmer, New York City, Dr Thomas Parran, Surgeon General, U S Public Health Service, Dr O H Perry Pepper, Philadelphia, Dr Charles R Reynolds, Surgeon General, U S Army, Dr P S Rossiter, Surgeon General, U S Navy, Dr Harold Rypins, Albany, N Y, Dr J F Siler (M C), U S Army, Dr J Gurney Taylor, Milwaukee, Wis

Dr Wilmar M Allen (Fellow) has been appointed Director of the Hartford (Conn) Hospital

Dr Herman M Baker (Fellow), Evansville, Ind, has been made President-Elect of the Indiana State Medical Association for 1937

Dr James B Collip (Fellow), Professor of Biochemistry, McGill University Faculty of Medicine, Montreal, will deliver a lecture on "The Significance of Recent Studies on the Anterior Pituitary and Related Glands," April 16, 1937, this being one of a series of lectures sponsored by the William Harvey Society of Tufts College Medical School, Boston

The third annual symposium at Duke University School of Medicine, Durham, N C, was held during October on diseases of the heart, circulation and kidneys Fellows of the American College of Physicians included among the speakers were Drs Warfield T Longcope and Louis Hamman, Baltimore, Dr Carl J Wiggers, Cleveland, Dr Charles C Wolferth, Philadelphia, Dr Frank N Wilson, Ann Arbor, Dr William deB MacNider, Chapel Hill, Dr James Edwin Wood, Jr, Charlottesville, Va, Dr William B Porter, Richmond, Va, Dr Stewart R Roberts, Atlanta, and Dr Soma Weiss, Boston

Dr Charles E Sears (Fellow), Portland, has been elected a Vice-President of the Oregon State Medical Society

Dr Walter F Donaldson (Fellow), Pittsburgh, has been reelected Secretary of the Medical Society of the State of Pennsylvania

The bulk of an estimated estate of more than \$200,000 has been bequeathed by the late Frances T Kinsey to the University of Pennsylvania to support and develop the Gastro-Intestinal Clinic at the University Hospital, under the direction of Dr Thomas Grier Miller (Fellow), or for such other activities in this field as he may desire

Dr Samuel B Scholz, Jr (Fellow), Philadelphia, has been elected a vice-president of the Association of Life Insurance Medical Directors of America

Dr Henry W F Woltman (Fellow), Rochester, Minn, has been elected President of the Central Neuropsychiatric Association

Dr Edward A Strecker (Fellow), Philadelphia, has been appointed a member of the advisory committee of the Friedsam Foundation, in connection with its program of research in child neurology. The research program will include studies of (1) organic and functional diseases of the nervous system in children, (2) neuroses and psychoses in early life, and, (3) social personality and home problems. The program will be carried on through grants and scholarships to research workers throughout the world. Only original work that promises to be fruitful of results will be considered. The applicant must state specifically the problem under investigation and the methods to be pursued. The Council of the Foundation will publish the results from year to year.

Dr Herbert L Bryans (Fellow), Pensacola, Fla, has been elected a Vice-President of the Gulf Coast Clinical Society

Dr Gordon B Myers (Associate), Detroit, has been appointed Professor and acting head of the Department of Medicine of Wayne University College of Medicine. Dr Hugo A Freund (Fellow), Detroit, has been appointed Professor of Clinical Medicine

Dr Eugene M Landis (Fellow), Philadelphia, gave the second Harvey Society Lecture at the New York Academy of Medicine, November 19, on "The Passage of Fluid Through the Capillary Wall"

Dr George R Minot (Fellow), Professor of Medicine, Harvard University Medical School, Boston, delivered the sixth Walter M Brickner Lecture at the Hospital for Joint Diseases, New York City, November 19, on "Anemia Etiology, Diagnosis and Treatment"

Dr Soma Weiss (Fellow), Boston, was guest speaker at the joint meeting of the Cincinnati Academy of Medicine and the Heart Council of Greater Cincinnati,

recently, his subject being "The Relation of the Cardiovascular System to the Nervous System"

As a memorial to the late Dr James M Anders (Master), Philadelphia, the Philadelphia County Medical Society devoted its meeting of November 25 to the observance of the annual Pennsylvania Health Day, a movement primarily sponsored in its beginning by Dr Anders Dr George E Pfahler (Fellow), Philadelphia, delivered a tribute to Dr Anders, and Dr Baldwin L Keyes (Associate), Philadelphia, presented a report of the Society's noise abatement committee, whose work was one of the last activities sponsored by Dr Anders before his death last August

Dr Elliott P Joslin (Fellow), Boston, is President of the Interstate Post-Graduate Medical Association

Dr Byrl R Kirklin (Fellow), Rochester, Minn, is President-Elect of the American Roentgen-Ray Society Dr Charles A Waters (Fellow), Baltimore, now occupies the Presidency

Dr John H Wyckoff (Fellow), New York City, recently assisted in the presentation of a symposium on sterilization before the section of obstetrics and gynecology of the New York Academy of Medicine

Dr Ray M Balyeat (Fellow), Oklahoma City, and Dr Hal M Davison (Fellow), Atlanta, were guest speakers on the program of a clinical congress held during the past autumn by the Chattanooga and Hamilton County (Tennessee) Medical Society

In honor of his thirty-three years of service to organized medicine, Dr Rock Sleyster (Fellow and Governor for Wisconsin), Wauwatosa, Wis, was tendered a dinner by the Medical Society of Milwaukee County at the Wisconsin Club, Milwaukee, on November 14 Dr Arthur J Patek (Fellow), Milwaukee, was toast-master Dr J Gurney Taylor (Fellow), Milwaukee, was one of those delivering an address Dr Sleyster is Chairman of the Board of Trustees of the American Medical Association In 1903 he became Secretary of the Calumet County Medical Society, holding the post for six years In 1910 he was elected Assistant Secretary of the State Medical Society of Wisconsin and its Secretary in 1914, holding this appointment until 1923 In 1924 he was elected President of the State Society, and since 1925 he has been its Treasurer From 1918 to 1923 Dr Sleyster was Editor of the Wisconsin Medical Journal He served as delegate to the American Medical Association from 1915 to 1926, and for the last four years of that period he was Vice Speaker of the House of Delegates He has been a Trustee since 1926 and Chairman of the Board since 1935 He graduated from the University of Illinois College of Medicine, Chicago, 1902 At present he is medical director of the Milwaukee Sanitarium

Dr Francis E Harrington (Fellow), Minneapolis, has been reelected Secretary of the International Society of Medical Health Officers

The Alumni Association of the College of Medical Evangelists, Los Angeles, held its third annual postgraduate assembly in Los Angeles, December 6. Among the speakers were Dr James F Churchill (Fellow and Governor for Southern California), San Diego, "A Discussion of Cardiac Drugs and Their Uses", Dr Alvin G Foord (Fellow), Associate Professor of Pathology, University of Southern California School of Medicine, "Laboratory Diagnosis for the General Practitioner", and Dr William J Kerr (Fellow and Regent), Professor of Medicine, University of California Medical School, "Obesity and Its Complications".

Dr William B Castle (Fellow), Boston, addressed the graduate teaching clinic of the Central Maine General Hospital, Lewiston, Maine, December 18, on "Development of the Knowledge of Vitamin Deficiency Diseases".

Dr Bernard Fantus (Fellow), Chicago, was a guest speaker on the program of the joint meeting of the Wayne County Medical Society and the Detroit Retail Druggists Association, December 7, when the newly revised Pharmacopoeia and the National Formulary were discussed.

Dr William M Donald (Fellow), Professor and Head of the Department of Medicine, Wayne University College of Medicine, Detroit, was a guest of honor at a joint meeting of the staff of the Receiving Hospital and the medical faculty recently, in recognition of his many years of service to both institutions. Dr Donald is seventy-six years of age and has been a member of the teaching staff of his alma mater since 1889. He was President of the Wayne County Medical Society in 1922 and has been a Fellow of the American College of Physicians since 1917.

Dr Sydney R Miller (Fellow and Regent), Baltimore, and Dr Leander A Riely (Fellow and Governor for Oklahoma), Oklahoma City, have been elected Vice-Presidents of the Southern Medical Association.

Dr Henry A Luce (Fellow), Detroit, was one of the speakers on a panel discussion of the relation of social security to the practice of medicine, sponsored by the medical economics committee of the Wayne County Medical Society and the Michigan State Medical Society, December 9.

Dr James H Black (Fellow) has been promoted to Professor of Clinical Medicine (Allergy) on the Faculty of Baylor University School of Medicine, Dallas.

Dr George R Minot (Fellow), Boston, on December 1 at the Waldorf-Astoria Hotel, New York City, received the annual award for research in the field of nutrition leading to the prevention of disease and the advancement of health, the award being made by the Associated Grocery Manufacturers Association of America.

Dr Hugh S Cumming (Fellow), formerly Surgeon General of the U S Public Health Service, was Chairman of the local Committee on Arrangements for the

second National Conference on College Hygiene, held in Washington December 28 to 31

Dr Cumming was presented with the Marcellus Hartley Gold Medal "for eminence in the application of science to the public welfare" at the annual meeting of the National Academy of Sciences, in Chicago during November

Dr Earl B McKinley (Fellow), Dean and Professor of Bacteriology, George Washington University School of Medicine, is on sabbatical leave, dating January 1, for a trip to the Orient, where he will conduct research on leprosy under the auspices of the American Leprosy Foundation, formerly the Leonard Wood Memorial. Dr McKinley will later continue his travels around the world, gathering material concerning the geographic distribution of disease for inclusion in a new book now in preparation, "A Cartography of Disease"

Dr Charles Franklin Craig (Fellow), Professor of Tropical Medicine, Tulane University of Louisiana School of Medicine, New Orleans, delivered the annual oration of the Smith-Reed-Russell Society, George Washington University School of Medicine, Washington, D C, on "Factors Influencing the Transmission of Malaria," during November

Dr James S McLester (Fellow and ex-Regent), Birmingham, Ala, has been appointed Professor of Medicine at the University of Alabama School of Medicine. Dr Edgar Gilmore Givhan, Jr (Associate) and Dr James B McLester (Associate) have been appointed Associate Clinical Professors of Medicine

Dr Thomas B Magath (Fellow), Rochester, Minn, has retired as Editor of the "American Journal of Clinical Pathology," after serving six years. Dr Robert A Kilduffe of Atlantic City, N J, succeeds Dr Magath as Editor

Dr Charles A Doan (Fellow), Professor of Medicine and Medical Research, Ohio State University College of Medicine, has been appointed Chairman of the Department. Dr George T Harding, III (Fellow), is Assistant Clinical Professor of Medicine (Psychiatry), and Lt Col Frank H Dixon (Fellow), Medical Corps, U S Army, is Professor of Military Science

Dr Lee Rice (Fellow), San Antonio, Tex, is President of the Texas Club of Internal Medicine

Dr Porter P Vinson (Fellow), Rochester, Minn, has been appointed Professor and Head of the Department of Bronchoscopy, Esophagoscopy and Gastroscopy at the Medical College of Virginia, Richmond. He will also be in charge of chronic pulmonary diseases at the Memorial Hospital

Dr David P Barr (Fellow and Regent), St Louis, has been elected President of the Central Society for Clinical Research

Dr Charles H McEnerney (Fellow), Washington, D C, has been reelected Secretary of the American Society for the Study of Arthritis

Dr Leroy S Peters (Fellow), Albuquerque, N M, has been made President-Elect of the southwestern Medical Association Dr Howell S Randolph (Fellow), Phoenix, Ariz, and Dr Orville E Egbert (Fellow), El Paso, Tex, have been elected Vice-President and Secretary respectively

Dr N M Marr (Associate), St Petersburg, Fla, has been elected President of the Pinellas County (Florida) Medical Society

Dr A Clayton McCarty (Fellow), Louisville, Ky, has been elected President of the Jefferson County (Kentucky) Medical Society

Dr George A Gray (Associate), Abilene, Tex, has been appointed Director of the Nolan County Health Unit

Dr R M Wylie (Fellow), Huntington, W Va, has been elected President of the Cabell County (West Virginia) Medical Society

OBITUARIES

OSKAR KLOTZ, M B , M D , F R C P (C) , F A C P , F R S C ,
1878-1936

THOSE who knew Oskar Klotz well find it difficult to express to others their full appreciation of the man. Widely known as a research worker and teacher, studying, investigating, directing and advising, with his activities spread over three continents, he became an authority in many of the departments of his chosen field of pathology. To his associates he was a great source of inspiration. With a remarkable ability to apply his knowledge whether from his own or other source, he was peculiarly fitted for the study of special problems in the origin of disease, its manifestations and its effects. The appended outline of his preparatory and postgraduate education, his various appointments, his memberships and offices held in national and international societies bespeak his wide variety of interests, the recognition by his fellow workers of his ability and genius and the high esteem in which he was held by men with whom he came in contact in his many spheres of activity.

Many tributes have been paid to him and to his work perhaps none more speaking than that from the Sisters of Mercy in Pittsburgh, who learning of his death sent the message that they could never forget the aid he gave them in the development of their hospital. Night after night was given freely to them during his busy life in that city, after days of labor in the University and its laboratories.

His contributions to medical literature number over one hundred titles. His studies of disease of the circulatory system made him an international authority. In tropical diseases he became one of the leaders. In his University he developed departments which proved him a great administrator. His library contained all that was important of the new and the most valuable of the old. His studies, his writings, his reading gave evidence that he appreciated the historical approach to questions under investigation. His grasp of any subject was wide, his early death means the loss of many important contributions to historical medicine.

His papers based on such reading were written in faultless English, and in such a style as to make him one of our outstanding essayists. I have frequently found myself looking upon him with Welch and Warthin as the three admirable, lovable pathologists of our time.

He was born in Ontario of Danish stock from Kiel, Holstein. His father was Chief Astronomer of the Dominion Observatories, a graduate of the University of Toronto and of Michigan, whose achievements won world wide fame. Two brothers, one of whom pre-deceased him, also graduated in medicine at the University of Toronto.

The funeral on November 15 was from Osler Hall of the Academy of Medicine, Toronto, where he presided last year. The service was conducted by Dr H J Cody, President of his University, and by Sir Robert Falconer, President Emeritus, in the presence of the Lieutenant Governor of the Province, representatives of the National Research Council at Ottawa, his colleagues in Pittsburgh and The University of Toronto, most of the Fellows of the Academy, and many of his students and friends.

To his wife, Stella M Scovill, who survives him, this College extends its sincerest sympathy.

Oskar Klotz, M B, M D, C M Born, January 21, 1878, at Preston, Ont. Attended Ottawa Collegiate Institute and the University of Toronto (M B, 1902), M D, C M, Faculty of Medicine McGill University, 1906. Postgraduate study at the University of Bonn, Bonn, Germany, 1905, University of Prague, Prague, Bohemia, 1905, University of Freiburg, Freiburg, Germany, 1908, University of Marburg, Marburg, Germany, 1914, house physician, Ottawa General Hospital, 1902-03. Governor's Fellow in Pathology, McGill University, 1903-05, Fellow in Pathology, Rockefeller Institute 1905-06, demonstrator in Pathology and Bacteriology, McGill University, 1905-07, assistant pathologist, Royal Victoria Hospital, 1905-10, pathologist, Maternity and Alexandra Hospitals, Montreal, 1905-10, lecturer in Pathology, McGill University, 1907-10, professor of Pathology and Bacteriology, University of Pittsburgh, 1910-20, director, Magee Pathology Laboratory, Pittsburgh, 1910-20, professor of Pathology, Faculdade de Medicina, Sao Paulo, Brazil, 1920-23, professor of Pathology and Bacteriology, University of Toronto, 1923 to date, director of pathology laboratories, Toronto General Hospital, 1923 to date, consulting pathologist, Hospital for Sick Children, 1923 to date, at one time a special member, Yellow Fever Commission, Rockefeller Foundation, member, Zeta Psi, Nu Sigma Nu and Alpha Omega Alpha Fraternities, past president of American Association of Pathologists and Bacteriologists, International Association of Medical Museums, Academy of Medicine of Toronto and Society for Experimental Pathology, member of council of National Research Council of Canada, American Association of the History of Medicine, Ontario Branch of St John's Ambulance Association and the Royal Canadian Institute of Toronto, member, Toronto Health League, Ontario Medical Association, Canadian Medical Association, Royal Society of Canada, Royal College of Physicians and Surgeons of Canada, Cancer Commission and chairman of subcommittee on Cancer Research (Ontario), International Association of Geographical Pathology (joint chairman for Canada), International Society for the History of Medicine, Medical Advisory Committee in conjunction with Ontario Crippled Children, Pathological Society of Great Britain and Ireland, Society for Experimental Biology and Medicine, Society for Tropical Diseases, American Society of Parasitologists, American Society of Tropical Medicine, Association of American Physicians and the American College of Physicians (Fellow, 1924).

JABEZ H ELLIOTT, M B, F A C P,
Governor for Ontario

DR WILLIAMS McKIM MARRIOTT

Dr Williams McKim Marriott, Fellow, died in San Francisco, November 11, 1936. He had only recently come to San Francisco from Washington University Medical School to assume the duties of Professor of Research Medicine and Dean of the Medical Faculty of the University of California.

Dr Marriott was born in Baltimore, Md, March 5, 1885. He received his B S degree from the University of North Carolina, 1904, and the degree of M D from Cornell University in 1910. He served as Assistant in Biochemistry in Cornell University from 1904 to 1907 and Instructor in Biological Chemistry, Washington University, 1910 to 1914. In 1914 he went to the Johns Hopkins Medical School as Instructor and Associate in Pediatrics, remaining until 1917, when he returned to Washington University, St Louis, as Professor of Pediatrics, which position he held until July 1936, when he came to San Francisco. From 1923 until his resignation in 1936, he was Dean of the Medical Faculty of Washington University. As Professor of Pediatrics he became Pediatrician in Chief, Barnes Hospital, St Louis Maternity Hospital and Washington University Clinics. He also held the title of Physician in Chief of St Louis Children's Hospital.

During his academic career he was honored by the following lectureships: In 1920, Harvey Society Lecturer, New York, 1921, Packard Lecturer, Philadelphia, 1925, Lecturer, Chicago Institute of Medicine, 1927, Annual Lecturer, San Diego Academy of Medicine, 1932, Visiting Lecturer, University of California Medical School, and Lecturer, California Academy of Medicine, San Francisco.

The following list of society memberships and offices indicates the breadth of his medical interests as well as the recognition which his position in the profession merited: Fellow of the American College of Physicians, Regent from 1926 to 1929, Vice-President, 1929 to 1930. Fellow of the American Medical Association, member of the Council on Pharmacy and Chemistry and member of Foods Committee. Member of the Council American Pediatric Society. President of the St Louis Pediatric Society. Member of Council American Society of Clinical Investigation. Association of American Physicians, American Society of Biological Chemists, American Association for the Advancement of Science, Society of Experimental Biology and Medicine, Harvey Society of New York (Honorary Member), American Academy of Pediatrics, Southern Medical Association, Chairman of the Sections on Medical Education and on Pediatrics.

He was a member of the Phi Beta Kappa and Alpha Omega Alpha honorary societies and served on the Editorial Boards of the *American Journal of Diseases of Children*, *American Heart Journal* and the *Journal of Clinical Investigation*.

Dr Marriott's contributions to medical and biological chemical literature were prolific and could not very well be mentioned here, including, as they do, two books, one concerning the relationship of biological chemistry to medical practice, and one on Infant Nutrition. Sections dealing with Pediatrics, in four books and over 80 contributions in the form of articles on biological chemistry and pediatrics.

With this remarkable background, an outstanding figure in American Medicine, Dr Marriott came to California to devote his time and energy

to research medicine and to the Deanship of the University of California Medical School. Before he was well settled in his new environment, his health became impaired by a chronic appendiceal abscess, which was treated surgically, but a blood stream infection ensued, eventually causing his death.

In Dr Marriott's death the American College of Physicians has lost one of its distinguished and loyal members. We in California have lost a warm friend and fellow worker, whose life with us was all too brief.

ERNEST H. FALCONER,
Governor for Northern California

DR WILLIS FASTNACHT MANGES

Willis Fastnacht Manges, M D, D Sc, was born in Luthersburg, Clearfield County, Pa, on December 4, 1876, and died in the Jefferson Medical College Hospital, Philadelphia, on November 24, 1936, of coronary thrombosis after a mercifully brief illness.

Dr Manges attended Gettysburg College, Gettysburg, Pa, and the Philadelphia College of Pharmacy before entering the Jefferson Medical College from which institution he received his M D degree in 1903.

After completing his internship in the hospital of the Jefferson Medical College, Dr Manges became actively associated with the Department of Roentgenology of the same College and Hospital, and in this Department he spent the greater part of his professional life in helpful, progressive work, research, study and in teaching.

Dr Manges entered the field of Roentgenology in the pioneer period of that branch of medical science and lived to become one of its foremost authorities. Dr Manges was fortunate, early in his professional career, to be intimately associated with such masters of medical science as W W Keen, J Chalmers Da Costa, George E de Schweinitz, Chevalier Jackson, Thomas McCrae and other like minded men of medicine who possessed, in addition to their medical knowledge, inspiring and stimulating personalities and who were never content with superficialities, but who sought and encouraged others to seek ultimate truth.

When the World War came, Dr Manges felt it to be his duty to abandon a lucrative and interesting practice, an assured professional and social position and, far more important and difficult for him, to leave his young wife and baby for the uncertainties and vicissitudes of army medical life. Dr Manges established, for the medical department of the Army, an efficient training school for roentgenologists at Camp Greenleaf, Fort Oglethorpe, Ga, that commanded the respect and admiration of the medical world. Many medical officers assigned for duty in the school for roentgenologists received from Dr Manges not only excellent technical training but inspiration for making roentgenology a life work.

After the war the intimate association of Dr Manges with Dr Chevalier Jackson's epoch making studies of the abnormalities and disorders of the air

passages brought about Dr Manges' outstanding contribution in this field, namely, a practical method of detecting the presence of non-opaque foreign bodies in the lower air passages

In 1928 Dr Manges was made Professor of Roentgenology at the Jefferson Medical College in well deserved recognition of the years of altruistic service rendered the medical school in giving inspiring instruction to both undergraduate and graduate students

Dr Manges was elected to Fellowship in the American College of Physicians in 1930 for, unlike many specialists in medicine, Dr Manges was a skilled and understanding physician. His specialty was roentgenology and he limited his actual practice to this field of endeavor but, fortunately for his patients, for his colleagues and for his students, Dr Manges held an active interest in clinical medicine and its problems. Modest to the degree of self effacement, Dr Manges was time and again advanced by the unanimous vote of his professional colleagues to positions of honor in the profession

He was President of the Philadelphia Roentgen Ray Society as well as Secretary, and, later, President of the American Roentgenological Society, and was active and interested in every association that he felt was helpful for the common good of the medical profession

Willis Manges possessed, by virtue of fortunate heredity and entirely natural characteristics, an unusually attractive, admirable and lovable nature. He was unselfish, generous, and interested in helping others. Charitable to the faults and weaknesses of others, he maintained the highest standards of living and thinking in his own life, and commanded the respect and admiration of all who came in contact with him or with his work

Dr Manges is survived by his widow, who was Marie Elizabeth Bosley of Baltimore, and two sons, Willis E and William Bosley. The College has lost a loyal, altruistic and helpful Fellow, the world, a kind, skilled and considerate physician, but no mere words can begin to express what the passing of Dr Manges means to those near and dear to him. One can, however, be thankful that as long as the sons of Dr Manges live, or their descendants, the qualities and characteristics that he so nobly exemplified cannot be lost to the world

E J G BEARDSLEY, M D, F A C P,
Governor for Eastern Pennsylvania

DR MATTHEW A DeLANEY

Brigadier General Matthew A DeLaney (Fellow) of the Army Medical Corps Retired, who served as White House physician during the Taft Administration, died November 1, 1936, at Walter Reed General Hospital, Washington, D C. He had been a patient at that hospital for about two months

From 1931 until his retirement, General DeLaney was one of the As-

sistant Surgeons General His last tour of duty was in command of the Medical Field Service School at Carlisle Barracks, Pennsylvania

Less than a month after the United States entered the World War General DeLaney went to France to command the Pennsylvania Base Hospital No 10 Early in 1918 he was appointed Liaison Officer to the British War Office, London

A native of Waymart, Wayne County, Pennsylvania, where he was born March 6, 1874, General DeLaney was graduated from Pennsylvania Normal School and obtained his medical degree from the University of Pennsylvania in 1898 In 1902 he was graduated from the Army Medical School

General DeLaney had also taken a course at the University of Vienna in 1913-14, and held a Certificate of Public Health from Harvard University Dickinson College, Pennsylvania, last year made him an honorary doctor of science

General DeLaney served in the Philippine Insurrection He was White House Physician from 1909 to 1913 He served on the Mexican Border in 1916 When the World War was ended he became Executive Officer in the Office of the Surgeon General In 1921 he was named Surgeon of the Field Artillery School at Fort Sill, Oklahoma, and in 1927 was ordered to assume the same duties at Camp Devens, Massachusetts The following year he became medical adviser in public health and sanitation, first, to Henry Stimson, and then to Dwight W Davis, who were in turn Governors General of the Philippines In 1931 General DeLaney was ordered to Command Carlisle Barracks, his last station before retirement

In addition to his being a Fellow of the American College of Physicians, he was a member of the American Public Health Association, a Fellow of the American Medical Association and of the American College of Surgeons He contributed many articles to medical journals Military honors accorded General DeLaney include the Distinguished Service Medal from the United States and the Order of St Michael and St George of Great Britain Field Marshal Douglas Haig mentioned him in dispatches for "gallantry on the field" He was a member of the Order of St Lazare of Jerusalem

He belonged to the Metropolitan, Chevy Chase and Army and Navy Clubs of Washington, and the Army and Navy and Polo Clubs of Manila

Surviving General DeLaney is his wife, Mrs Elizabeth V DeLaney, who makes her home in Washington

CAPTAIN OWEN J MINK

Captain Owen J Mink, Medical Corps, U S Navy, the Assistant Chief of the Bureau of Medicine and Surgery, died suddenly at his home at Chevy Chase, Maryland, on October 21 Captain Mink was born at Pectone, Illinois, April 26, 1879, so was 57 years of age at the time of his death He graduated from the Medical School of the University of Michigan in 1903 and was appointed Assistant Surgeon in the Navy June 7, 1904 His

home then was at Wheaton, Illinois. He was promoted Passed Assistant Surgeon June 7, 1907, Surgeon August 29, 1916, Commander July 1, 1918, and Captain, Medical Corps, October 2, 1925.

His first duty was at the Naval Hospital at Philadelphia, following which he received a postgraduate course of instruction in naval medicine at the U S Naval Medical School, completing this postgraduate course in the spring of 1905.

The types of duty performed by Captain Mink were of a most varied character and he held many important posts both afloat and ashore. In 1910 he was a member of the board to study and report upon the causes and prevention of typhoid fever in the Navy and he was a pioneer in the movement to introduce typhoid vaccination in the Navy. After this he served on the U S S West Virginia, then a member of the famous armoured cruiser squadron. During the World War he was on duty at the Naval Training Station, Great Lakes, Illinois. After the war he served as Executive Officer of the U S Naval Hospital, Great Lakes, Illinois, and as Senior Medical Officer in Samoa and later as Senior Medical Officer in the Virgin Islands and Commanding Officer of the Naval Hospital at Saint Thomas. He then served as Commanding Officer of the Naval Hospital at Canacao, P I.

From 1931 to 1933 he was Chief of the Division of Preventive Medicine in the Bureau of Medicine and Surgery. He was appointed Assistant Chief of the Bureau of Medicine and Surgery June 26, 1933.

Captain Mink was an outstanding medical officer of the United States Navy and was particularly distinguished in the fields of bacteriology and preventive medicine. Few men in this country surpassed him in point of knowledge of preventive medicine and public health, particularly in respect to the simple and homely common sense with which he applied this knowledge to the problems of disease prevention. The editor of the Journal of the Royal Army Medical Service quite recently in requesting permission to reprint an article on disease prevention written by Captain Mink, commented on its great value and the many practical features which it contained.

Captain Mink had a most likeable personality. Pleasant, sincere and unaffected, everyone who came in contact with him loved and admired him. He was very fond of flowers and was an ardent amateur gardener. Captain Mink is survived by his wife and three children. His death is a real loss not only to his family and friends but to the Medical Corps and the Naval Service.

P S ROSSITER, M D , F A C P ,
Surgeon General, U S Navy

DR THOMAS CRAIG REDFERN

Dr Thomas Craig Redfern (Fellow), Winston-Salem, N C, was born in Chesterfield County, S C, July 31, 1892. He received his academic training at Clemson College, graduating with the degree of B S in 1912, and receiving his M D in 1916 from the Long Island College Hospital. After serving his internship there, he was for two years assistant surgeon in the United States Medical Corps, followed by a residency in medicine in Barnes Hospital, St Louis.

He became medical director of the City Memorial Hospital, Winston-Salem, N C, in 1920, and Chief of the medical service of that hospital from 1924 to 1931. He was likewise Chief of the Medical Service of the North Carolina Baptist Hospital from 1923 to 1931. From 1924 on, Dr Redfern became an outstanding internist in his community, and besides serving on the staffs of the two hospitals mentioned, was a member of the Governing Board of the Forsyth County Tuberculosis Sanatorium, former President of the Forsyth County Medical Society, and a member of the North Carolina State Medical Society and of the Southern Medical Association, and a Fellow of the American Medical Association, as well as of the American College of Physicians. He was a former member of the Rotary Club and a member of the First Presbyterian Church.

August 15, 1936, he had a coronary thrombosis, succeeded by embolic phenomena, which caused his death from myocardial failure nine weeks later.

Dr Redfern was a leader in his chosen field in his city, always studious, an original thinker, and a man of lovable character. He is survived by his widow and a son and daughter.

CHARLES H COCKE, M D, F A C P,
Governor for North Carolina

DR THOMAS DEWITT GORDON

Thomas Dewitt Gordon (Fellow), of Grand Rapids, Michigan, died November 20, 1936, of coronary disease, aged 56.

Dr Gordon was born in Maxwell, Ontario, on November 1, 1880. Graduating from the University of Michigan Medical School in 1909, he came to Grand Rapids to practice in 1911 directly from the University Hospital where he had been first assistant in Internal Medicine.

Dr Gordon early offered his services to his country in the World War, and with the rank of Captain, organized and took over-seas Ambulance Unit Number 339. Detached over-seas, he became Chief Sanitary Officer of the 85th Division. Returning from the war he again took up his general practice, but soon determined to limit his work entirely to pediatrics in which he was much interested and for which he prepared by postgraduate work both in this country and abroad. In this special work for which he was so well suited, he developed an enviable reputation throughout the state.

Markedly competent and well trained, with a pleasing personality, he was much beloved and appreciated by his patients and his professional brothers. A forceful speaker, with a teacher's ability to handle his subject, he added much to professional discussion and was always in demand for talks on his chosen specialty.

The disease from which he died manifested itself two years earlier and compelled a prolonged absence from his work. He bore his affliction with great philosophy. Some six months before he died he thought himself sufficiently recovered to take a few months postgraduate work and return to practice. Within a few weeks of his return he was again going at full tilt, as was his custom, but the demands of practice soon resulted in a return of symptoms.

Dr. Gordon was an active member of the Blodgett Hospital Staff, an ex-president of the Kent County Medical Society, and a member of various pediatric societies. He had been a member of the American College of Physicians since 1919. Lovable, conscientious, always dependable, the profession has lost a valued member, a wise councillor and friend.

BURTON R. CORBUS, M.D., F.A.C.P.,
Grand Rapids, Mich.

DR. ARTHUR STERN

Dr. Arthur Stern (Fellow), Elizabeth, N. J., died suddenly November 28, 1936, of coronary thrombosis, aged, 68 years.

Dr. Stern was born in Geseke, Westphalia, Germany, in 1868. He received both his preliminary and medical education in his native Germany, but did not practice medicine there. After graduating from the Friedrich-Wilhelms University, and after passing his State Board examination at Munich, he joined the Hamburg-American Steamship Line as ship surgeon, and made five trips in that capacity across the Atlantic. In 1892, he came to Elizabeth, N. J., and began the practice of medicine and surgery. His fame grew sufficiently to justify his specializing in Pediatrics, which he pursued until his death. At the time of his death he held many responsible hospital positions. He was Senior Attending Physician at the Elizabeth General Hospital and Senior Attending Pediatrician at the St. Elizabeth Hospital, both of Elizabeth, N. J.

Dr. Stern became a Fellow of the College on January 30, 1920. He had been a president of the Union County Medical Society and a vice-president of the New Jersey Pediatric Society. He was a Fellow of the New York Academy of Medicine, the American Medical Association and a member of the American Child Hygiene Association. He had published numerous articles.

In Dr. Stern's death, the people of Elizabeth, the profession and the College, have suffered an irreparable loss.

CLARENCE L. ANDREWS, M.D., F.A.C.P.,
Governor for New Jersey

DR JACOB C ATWELL

Following an illness of but two days, Dr Jacob Clinton Atwell (Fellow) of Butler, Pennsylvania, died on November 2, 1936, of pneumonia

Dr Atwell was born in Boyers, Butler County, March 25, 1874. He received his early education in the local public schools and later attended the Slippery Rock State Normal School and the West Sunbury Academy. In 1898 he graduated from the Medico Chirurgical College in Philadelphia, and immediately after established his office in Butler where he became one of the most prominent physicians in the county and where he practiced until the time of his death.

Dr Atwell was a member of the First United Presbyterian Church and took an active interest in the affairs of the church, having been a member of the United Presbyterian Sessions since 1912.

He was an Associate Member of the Pittsburgh Academy of Medicine, a member of the Butler County Medical Society, the Pennsylvania State Society, a Fellow of the American Medical Association, and has been a Fellow of the American College of Physicians since 1912.

During the World War, Dr Atwell was First Lieutenant in the Medical Corps of the U S Army.

Surviving are his widow, Mrs Mollie Jennings Atwell, a daughter, Mrs Charles Midberry of Butler, a son, Jennings Clinton Atwell, Jr, of Butler, and several brothers and sisters.

E BOSWORTH MCCREADY, M D , F A C P ,
Governor for Western Pennsylvania

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TUBERCULOSIS OF THE PERICARDIUM, A STUDY OF TWENTY CASES

By CHESTER S. KEEFER, M.D., F.A.C.P., *Boston, Massachusetts*

TUBERCULOSIS of the pericardium is the least common and most serious tuberculous infection of the serous membranes. Generally speaking, it is infrequent, and since it has various clinical features which may not direct one's immediate attention to the pericardium, I am reviewing a series of 20 cases which were observed over a period of several years. The details of the cases are indicated in table 1.

ANALYSIS OF CASES

Age It is agreed that tuberculosis of the pleurae and peritoneum is most often seen between the ages of 15 and 40 years. Everyone who has studied tuberculosis of the pericardium remarks that it is found most frequently over 40 years of age.^{1, 2} This group of cases was no exception to that statement. Table 2 illustrates this very well. There were 17 men and three women.

Duration of Disease Of this group, 18 died and two survived. There were 17 necropsies in the fatal cases. Of those who died, it was sometimes difficult to determine the exact duration of the disease, but it was commonly found to be one month to one year after the onset of symptoms, the average duration being from two to four months.

Pathology In seven of the 20 cases there were signs of a large collection of fluid in the pericardium. In the others, the exudate was fibrinous and frequently measured 1 to 3.5 centimeters in thickness. In one there was calcification. Eleven of the cases showed enlargement and tuberculosis of the mediastinal lymph nodes. There was an associated tuberculosis of the lungs in three cases, of the pleura in seven cases, and of the peritoneum and epididymis, each in one. Four of the patients finally died of miliary

* Read before the Annual Meeting of the American Climatological and Clinical Association, Richmond, Virginia, October 27, 1936.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School, Boston, Mass.

TABLE I
Summary of Twenty Cases of Tuberculosis of the Pericardium

Symptoms	Physical Signs							Fever	W B C	Duration of Illness	Anatomical	Remarks
	Size of Heart (cm.)	Fric- tion Rub	Peri- cardial Fluid	Mur- murs	Arrhythmias	B P Systolic/ Diastolic	Edema					
Wasting Disease with Obscure Fever												
Progressive weakness 2 mos Loss of weight. Constrict- tion across chest 6 wks	10×7	+	0	0	0	144/66	0	100°-103°	5 900	3 mos	The lymph nodes The peri- carditis	
Loss of weight weakness fever mental confusion	12×3	0	0	0	0	130/88	0	99°-100 4°	16 500	?	The pericarditis The lymph adenitis of the tracheobronchial lymph nodes Chronic the with cavity	
Loss of weight weakness fever	12×3	0	0	0	0	?	0	Normal 101°-102 8°	18 000- 20 000	? 4½ wks on ward		
Fever, loss of weight and weakness	13×3	0	0	0		111/78	0	100°-102°	19 600	?	The epididymis Miliary the Obliterative fibrous pericarditis with calcification	Miliary the
Heart Failure with Congestion												
Dyspnoea 10 mos legs 5 mos	11 5×3	0	0	0	0	90/30	+ General ized	0	8 200	10 mos	Adherent pericardium The peri- carditis Rt hydrothorax Mil- itary the of lungs Asciates C P C of liver and viscera	Progressive heart failure Terminal miliary the, af- brile, ex anosis striking
Constriction in chest 2 mos Shortness of breath 2 mos Edema of legs 6 wks	12×4	0	0	0	0	135/90	+ General ized	0	11 000	2 mos	The bronchial and mediastinal lymph nodes The pericarditis and pleurisy Hypertrophy of heart Hydrothorax Asciates	Progressive heart failure on- set suggesting pericardial or coronary artery disease
Pain in chest and abdomen 1 mo Cough 1 mo Ab- normal swelling 3 wks	14×5	0	0	0	0	115/70	0	99°-103°	12,000	2 mos	The bronchial and mediastinal lymph nodes The pericarditis Dilatation of heart C P C of viscera	Great cardiac enlargement Pericardium varied from 2 5 to 3 5 cm in thickness at necropsy Miliary the
Pain in chest and abdomen 5 mos Shortness of breath 3 mos Edema 1 mo Precordial pain 1 mo	12×4	0	0	0	0	110/60	+ General ized	97°-100 4°	10 000	5 mos	The pericarditis The bronchial lymph nodes Miliary the of lungs pleurisy spleen liver As- ciates and bilateral hydrothorax	Febrile illness at onset fol- lowed by heart failure with- in 3 months
Pain in chest Dyspnoea cough swelling of abdomen and feet	12×3	0	0	0	0	110/80	+ Depen- dent	99°-102°	4 250	2½ mos	The of bronchial and mediastinal lymph nodes The pericarditis C P C of viscera	

No.	Sex	Falling health for 1 yr Dyspnea and constriction across chest 2 mos Cough 2 mos.	11×4	+ 2 wks	0	0 Faint heart sounds	Auricular fibrillation	105/75	+	99°-101°	7,400- 11,000	1 yr	Tuberculous pericarditis pleura—bilateral The tracheo- bronchial nodes	
10 81	♂	Faint in epigastrium and up- per part of left scapular re- gion 2 mos Dyspnea 2 wks Idem 1 2 wks	12×4	0	0 700 c c	0	Auricular tachycardia with partial heart block and dropped beats	134/110	Depen- dent	0	5 200	2 mos	The pericarditis Obstructive pleuritis Left hydrothorax The of bronchial and medias- tinal nodes	
11 50	♂	General malaise for 3 mos Idem of extremities 2 mos Dyspnea on exer- tion Orthopnea	13×4	0	+	Faint heart sounds	Sino auricular tachycardia Left ventricular preponderance	110/65	Depen- dent ascites	98 6°-101°	4 500	5 mos	The pericarditis with effusion (300 c c) Coronary arterio- sclerosis C P C of viscera	Miliary tbc
Pericardial Effusion														
13 24	♀	Pain in chest 1 mo	13 5×4	+	+	0 Faint heart sounds	0	105/75	0	09°-101°	4 200	6 mos	Pericarditis with effusion The of mediastinal lymph nodes Pleurisy with effusion	Recovered
14 49	♂	Pain and constriction in chest 1 mo Dyspnea 1 mo Loss of weight	15×7	0	+	Soft systolic m apex	0	126/87	0 Liver enlarged	09°-101°	12 600	1 mo	Pericarditis with effusion The of mediastinal lymph nodes Pleurisy with effusion	Pericardial cavity contained 3500 c c at necropsy
15 70	♂	Pain in left chest 2 wks Dyspnea 2 wks Idem of legs 2 wks	13×4	+	+	Faint heart sounds	0	110/80	Depen- dent Ascites	0°-100° 101°-102°	6 500	3 1/2 mos	The pericarditis with effusion Miliary tbc Pleural effusion, left	
16 22	♂	Shortness of breath Pain in chest	12×4	+	+	0	0	110/70	0	100°-101°	9,600	3 mos		Recovered Dextrocardia
17 52	♂	1 ever abdominal distention	10 5×9	0	+	0	0	115/90- 05/80	+	99°-101°	9 000	7 mos		The peritonitis The peri- carditis with effusion Ch- riosis of liver ?
Terminal														
18 46	♂	Sense of constriction across chest 3 mos	14×3	0	0	0	0	220/118	+	90°	14,400	3 mos	The pericarditis The mediasti- nitis Chronic nephritis	Terminal in hypertension with chronic nephritis
19 55	♂	Nausea and vomiting 3 wks Ascites 2 wks	12×3	0	0	0	+	80/50	Depen- dent Ascites	09°-101°	4 000- 15 000	7 wks	The pericarditis	Terminal in cirrhosis of liver
20 70	♀	Weakness and dyspnea 3 wks	11×3	0	0	0	Auricular fibrillation	105/65	0	08 6°-90 2°	12 500	3 wks +	The pericarditis Cirrhosis of liver Pulmonary tbc	Terminal in cirrhosis of liver

tuberculosis Thrombosis of the femoral vein and a pulmonary infarct were seen, each once

TABLE II
Age Distribution of Patients with Tuberculosis of the Pericardium

Age	Number of Cases
0-9	0
10-19	0
20-29	4
30-39	0
40-49	3
50-59	4
60-69	3
70-79	5
80+	1
Total	20

It would appear that tuberculosis of the pericardium may produce a massive effusion or a thick productive exudate. When death occurs at this stage, tuberculous tissue is abundant and easily recognized. When the lesion heals, there is organization of the granulation tissue with or without calcification.

Under the term primary tuberculosis of the pericardium, there are described cases¹ in which the pericarditis seems to be the oldest and, in some, the only tuberculous lesion found at necropsy. In the present series of cases, the lesion in the pericardium appeared to be the oldest in twelve. In several the pericardium had become involved as a result of a rupture of a caseous lymph node directly into the pericardial sac. In others, there was evidence that the process had extended to the pericardium from the pleura, the lung, or even the peritoneum. Since practically all infections of the serous membranes result from an extension of an infection directly to them, it is not surprising to find that pericardial tuberculosis arises in this way. When the lesion of the pericardium is the oldest one and the disease is confined to the pericardium, death results from the signs of a wasting disease or cardiac insufficiency, or it may be found accidentally during the course of another disease. Very often, however, the process spreads beyond the pericardium so that there is multiple serous membrane involvement or miliary tuberculosis. In these, the clinical picture is that of multiple serous membrane tuberculosis, cardiac insufficiency, or miliary tuberculosis, or all three. These various aspects of infection will be taken up separately.

GENERAL FEATURES

Fever The febrile reaction was a conspicuous feature in 13 of the 20 cases. It was the outstanding characteristic of the patients with only the signs of a wasting disease and equivocal pericardial signs. In the patients with circulatory failure with congestion, fever was absent in four of the

eight cases. In those with a pericardial effusion, only one remained fever-free during the period of observation. In two of the cases in which the condition was latent and therefore probably terminal, there was no fever. In the febrile cases the daily fluctuation ranged between 99° and 101° , 102° , or even 103° . In essence, then, the presence of irregular fever in patients with heart failure, especially elderly individuals with signs suggesting pericardial disease, should point toward the possibility of tuberculosis of the pericardium.

White Blood Cell Count Anemia was not a feature in these cases. The red blood count and hemoglobin content were reduced in four. In the others they were normal. One patient had chronic nephritis. As is the case in other types of tuberculosis, there was nothing absolutely characteristic about the total white blood cell count. There were wide variations. It was below 5,000 in five, between 5,000 and 10,000 in seven, 11,000 and 15,000 in five, and above 15,000 per cubic millimeter in three. There was nothing distinctive about the differential count although the lymphocyte-monocyte ratios were not studied in detail.

Cardiac Arrhythmias Auricular fibrillation was present in three cases, partial heart block in one. In the others, there were no detectable abnormalities by physical examination. It was not uncommon to observe a low voltage with inversion of the T-waves. Paroxysmal auricular fibrillation has been observed by Dillon,³ and others.⁴

Signs of Congestive Heart Failure There was peripheral edema in 10 cases, ascites in eight, and pleural effusion in nine. In seven of the nine cases of pleural effusion, it was finally demonstrated that tuberculous pleurisy was present, so that one was in fact dealing with multiple serous membrane infection. The pleural effusion was unilateral in five, bilateral in three, and interlobar in one. In two cases such effusions were present without peripheral edema or ascites. In both of these cases the pericardial involvement was indicated by a well marked friction rub, and in one the interlobar pleurisy with effusion was discovered only by roentgen-ray examination. In three cases the pleural effusion was due to venous stasis, as attested by the character of the fluid, and by the absence of tubercles in the pleura at necropsy. In one of these cases there was an effusion on one side due to venous stasis and a productive tuberculosis on the other side. In the remaining five cases, which include one of the previous group where both stasis and tuberculosis were present, there was tuberculosis of the pleura to account for the effusion.

Of the eight cases showing ascites, two showed no peripheral edema, in one the ascites was due to tuberculosis of the peritoneum. In six, the ascites was a part of the general edema.

Summing up, then, it can be asserted that the edema may be general. When there is an associated pleural effusion with or without peripheral edema, it is highly probable that there is an associated tuberculosis of the

pleura. This can usually be determined with precision by studying the aspirated pleural fluid.

When ascites exists it is seen most often in association with peripheral edema, and the fluid has the characteristics of a transudate. Much more rarely, the effusion is due to tuberculosis of the peritoneum, but one may see cases with evidence of heart failure, with tuberculosis of the pericardium and of the pleura, and with a transudate in the peritoneal cavity. Only after a careful study of the fluid can the final decision be reached. Predominant ascites as a manifestation of heart failure was present in only one case in this group.

Blood Pressure. In pericardial disease, especially when there is cardiac compression, it is not infrequent to find a low systolic blood pressure and a low pulse pressure, particularly when the signs are acute. If one excludes two cases in which there was an associated hypertension, the blood pressure in this group was normal or below the average accepted normal for the age group. The systolic pressures varied from 90 to 135 mm. of mercury, and the diastolic pressures from 50 to 88 mm. of mercury. It is obvious that there is nothing absolutely characteristic about the average blood pressure findings. More important in diagnosis is a gradually declining blood pressure with a small pulse pressure, in the face of a rising venous pressure. These are indications of cardiac compression and should direct one's attention to the pericardium.

Pulse Rate. Increase in the pulse rate was the rule, 100 to 120 per minute being common. This is understandable on two grounds: first, because the metabolic requirements are increased due to the infection and, second, because it is only by means of an increased rate that the heart can maintain the output per minute when there is a decrease in diastolic filling. Pulsus paradoxicus was noted on several occasions.

Local Signs Over the Pericardium. The points of diagnostic importance in the physical examination are the determination of the size and configuration of the heart, the presence or absence of a friction rub, the presence of arrhythmias or murmurs, and the quality of the breath sounds. In this group of 20 cases, the transverse diameter of the heart, as determined by roentgen-ray examination, varied from 14 to 22 centimeters. The most conspicuous widening was present in those individuals showing effusions, of which there were seven. True dextrocardia was existent in one. The amount of fluid varied from 700 to 3,500 cubic centimeters. A friction rub was heard in only five cases, and it persisted anywhere from two days to three weeks. The apex beat was either feeble or not obtainable, and the sounds distant and faint. Murmurs were absent, and arrhythmias were present in three cases. These signs then may be summed up by saying that the important ones are an increase in the transverse diameter of the heart, the signs of an effusion, a pericardial friction rub, and a feeble apex beat with distant heart sounds without murmurs.

Roentgen-Ray Examination There is nothing characteristic in the roentgen-ray findings. There may be the classical signs of a pericardial effusion or merely a widening of the cardiac shadow. The fluoroscopic examination may reveal a diminished pulsation of the ventricles. This is more significant when the size of the heart is small, since it indicates an interference with diastolic filling.

The Character of the Pericardial, Pleural, and Ascitic Fluid The fluid may be straw-colored or hemorrhagic. When there is a simple transudation of fluid due to venous stasis, the fluid has the characteristics of a transudate. There is one condition, however, in which a transudate assumes the characteristics of an exudate, insofar as the protein content is concerned, and that is following a copious diuresis that has been induced by drugs. I have seen the protein content of a pleural fluid increase from 1 to 4.5 per cent following diuresis. The circumstances under which the fluid is examined must therefore be taken into account.

The fluid may be hemorrhagic and, in this respect at least, resemble the fluid from rheumatic fever exudates, or from those resulting from metastatic tumors in the serous membranes. From experimental studies⁵ we know that hemorrhagic fluids in tuberculosis are more likely to contain tubercle bacilli, since large numbers of tubercle bacilli injected into the serous membranes of a sensitized animal frequently result in a hemorrhagic exudate.

The presence of tubercle bacilli as determined by guinea pig inoculation or by direct examination makes the diagnosis positive. Without this, the fluid findings are not absolutely decisive. The important point to determine is whether the fluid is an exudate or a transudate, since in tuberculosis of the pericardium there may be a transudate or an exudate in the other cavities depending upon the presence of infection, or stasis, or both.

The cell count is increased and the cells are usually of the mononuclear or lymphocytic variety.

Symptoms It is convenient for purposes of discussion to divide the cases into several groups, depending upon the symptomatology and the clinical course of the disease. This division is more or less arbitrary since one group may gradually begin to show the signs which are considered characteristic of another. This is not surprising since such merely indicate various phases of the same disease process. The outstanding clinical features depend upon the pathogenesis, mode of spread, the type of pathological process causing the functional disturbance, and the duration and stage of the disease. The following subdivision of cases has been adopted:

- 1 Patients with symptoms and signs of a wasting disease and obscure fever
- 2 Patients with symptoms and signs suggesting heart failure with congestion
- 3 Patients with symptoms and signs of multiple serous membrane tuberculosis

- 4 Patients with symptoms and signs of a massive pericardial effusion
- 5 Patients with symptoms and signs of miliary tuberculosis

PATIENTS WITH SYMPTOMS AND SIGNS OF A WASTING DISEASE AND OBSCURE FEVER

There were five patients in which these signs were the outstanding features of the illness. The following case report is an example.

Case 12 A man, aged 70 years, complained of shortness of breath and weakness. His past and family histories were inconsequential and he had always enjoyed relatively good health. For a period of two years he had felt some constriction across his chest after exertion which was relieved by rest. Aside from this, he had no discomfort until two months before he was seen. At that time he began to notice progressive weakness, loss of weight, insomnia, and some shortness of breath on exertion. Several days before admission to the hospital he had some pain over the lower part of the chest which was not severe and did not radiate. The examination showed an elderly man, with moderate dyspnea, resting quietly. There was no orthopnea. He obviously had lost weight but his skin and mucous membranes were of normal color. The positive findings were confined to the examination of the heart. There was some tenderness of the skin over the precordium, the heart measured 10 centimeters to the left and 7 centimeters to the right of the mid-sternal line by teleroentgenogram. The sounds were distant but without murmurs, and the apical impulse was feeble. A short superficial friction rub was heard over the precordium. The blood pressure was 145 mm. of mercury systolic, and 65 mm. of mercury diastolic. The lungs were clear, the abdomen and extremities negative.

Laboratory Examinations The electrocardiographic examination showed a normal mechanism with no abnormalities in conduction. There was no anemia, and the leukocyte count was 5,900 per cubic millimeter. The differential was normal.

Course of the Disease After two days, the pericardial friction rub disappeared and never returned. The temperature was elevated, and varied from 100° F. to 103° every day. The patient showed signs of progressive weakness and loss of weight. The blood pressure did not change, there were no signs of congestive heart failure or increased venous pressure. The area of cardiac dullness remained wide and the heart sounds became more and more distant until they could be heard with difficulty. The apex beat could not be felt. He finally had an attack of rapid heart rate with collapse and died in coma. The total duration of his illness was 12 weeks from the onset of symptoms. The necropsy showed a tuberculosis of the pericardium with thick fibrinous exudate. The heart was of normal size. There were numerous enlarged mediastinal lymph nodes, one had extended directly into the pericardial sac. There were no signs of active tuberculosis elsewhere.

In brief, then, the salient features were those of a febrile illness in an elderly man, with a transitory pericardial friction rub and an increase in the area of cardiac dullness, a feeble apex impulse and distant heart sounds. His course was one of progressive weakness with the features of a chronic febrile wasting disease. Necropsy demonstrated that the sequence of events had been the rupture of a caseous mediastinal lymph node into the pericardial sac and an extensive tuberculous infection of the pericardium. At no time were there any signs of increased venous pressure.

These patients have the symptoms and signs which are common to any

chronic infection (fever, progressive weakness, loss of weight, anorexia, malaise, etc.) In addition, there may be symptoms referable to the chest, with pain and constriction over the precordium and shortness of breath. The physical examination may reveal a pericardial friction rub, but the chief features may be signs which are compatible with a thickening of the pericardium, i.e., feeble apex beat, distant heart sounds, and an increase in the transverse diameter of the heart. In any event, it should be recalled that obscure fever in the elderly may be due to a tuberculosis of the pericardium.

PATIENTS WITH SYMPTOMS AND SIGNS OF CARDIAC INSUFFICIENCY

When there is a compression of the heart or great vessels resulting from an exudate in the pericardium, there is an obstruction to the inflow of venous blood, and circulatory failure with congestion follows. When pericardial disease appears in the elderly there is often another disease present, namely, coronary arteriosclerosis. The changes in the circulation which follow pericardial disease often increase the difficulty of supplying sufficient blood to the heart. The low mean arterial pressure, the low cardiac output, and low stroke volume will all tend to decrease coronary circulation. In addition, in some cases, as those reported by Bellet, Gouley, and McMillan,²⁰ there exists definite arteritis with occlusion of the coronary vessels which would naturally decrease the coronary circulation further. It is not surprising, then, that once circulatory failure sets in it is progressive and there is rarely any improvement. These patients complain of a sense of constriction in the chest on exertion that is relieved by rest. They exhibit edema, shortness of breath, cough, and progressive weakness. Early in the course of the disease there may be very little pulmonary congestion. The dyspnea in these cases is probably due in part to the increase in the venous pressure in the great veins through a reflex mechanism, as described by Harrison.⁷ Later, there are signs of pulmonary congestion. But, as I have stated, effusions into the pleural cavity in active tuberculosis of the pericardium are likely to be due to an infection of the pleura rather than a transudate. Finally, the disease is not infrequently terminated by a miliary tuberculosis. In this group of eight patients with progressive heart failure, there was fever in four, pleural effusion in seven, tuberculosis of the pleura in five, ascites with edema in six, and ascites without edema in one. Miliary tuberculosis was present in three. The following case illustrates the course of events in a typical case.

Case 9 This white man, 74 years of age, was seen first in December 1934. At that time he complained of failing health for two or three months. This was characterized by weakness, shortness of breath on exertion, orthopnea, and edema of the lower extremities, genitalia, and abdomen. He had always enjoyed good health until the present illness.

The physical examination showed a small man with evidence of loss of weight. The skin was dry and scaly over the upper part of the trunk and arms. The mucous membranes were of normal color. The examination of the head revealed no abnormalities. The neck veins were moderately distended. The chest was small, moved

as a whole, and showed a senile kyphosis. There were moist râles at both lung bases, and the signs of a hydrothorax in the left pleural cavity. The heart borders were difficult to define by percussion. The apex beat was not visible or palpable. The sounds were distant and feeble in quality. There were no murmurs or friction rub. The aortic second sound was louder than the pulmonic second sound. The abdomen was distended with fluid, and there was a distinct fluid wave on percussion. No other abnormalities were found. There was massive pitting edema over the sacrum and back, lower part of the abdominal wall, and genitalia. The temperature was normal, the pulse rate varied from 100 to 110 per minute. The respirations were 32 per minute. The blood pressure was 110 mm of mercury systolic, and 75 mm of mercury diastolic.

Laboratory Examinations The urine showed neither albumin nor sugar. The white blood cell count was 4,250 per cubic millimeter. The total protein of the blood plasma was 5.7 per cent. The ascitic fluid had the characteristics of a transudate. The specific gravity was 1.012. There were 23,000 cells per cubic millimeter, of which 500 were white blood cells and the remainder were erythrocytes. The differential count of the white cells showed 80 per cent lymphocytes and 20 per cent monocytes.

Roentgenogram of the chest showed the heart to be enlarged to the left, and there were signs of fluid at the left base. There was evidence of an old tuberculous process at both apices.

Electrocardiographic examination revealed a left ventricular preponderance with a low amplitude of the QRS complexes.

Course of Illness The patient failed gradually for a period of 11 weeks. The usual treatment for congestive heart failure was unsuccessful in relieving his edema. During the last week of his illness there were fever, cough, and an increase in the râles throughout his lungs. He died five months after the onset of symptoms of heart failure. The anatomical diagnoses were Tuberculosis of the pericardium—containing 300 c.c. of sero-sanguinous fluid, miliary tuberculosis of lungs, liver, spleen, coronary arteriosclerosis, cardiac enlargement.

To sum up, an elderly man developed heart failure with congestion which was progressive without remission over a period of five months. The entire course was afebrile except for the last week of his illness when there was irregular fever and cough. Necropsy demonstrated the cause of his illness to be due to tuberculosis of the pericardium and a terminal miliary tuberculosis.

MECHANISM FOR THE PRODUCTION OF CIRCULATORY FAILURE WITH CONGESTION IN PERICARDIAL DISEASE

From the careful observations of a number of observers, we are now able to understand the mechanism which produces circulatory failure in patients with pericardial disease. Experiments have been done on animals with acute and chronic pericardial disease,^{8, 9, 10} and quantitative studies of the circulatory functions have been carried out in man with the same disorder. The type of circulatory failure which is seen in pericardial disease has been called "inflow stasis" by Volhard.

In the case of an acute distention of the pericardium with an inflammatory exudate or with blood, the pericardium stretches very slowly so that

the increasing pressure within the pericardial sac causes cardiac compression, with a falling systolic blood pressure, a rising venous pressure, enlargement and depression of the liver Beck¹¹ has stated that a pressure equal to 16 centimeters of water, acutely applied to the heart, may be fatal This external pressure on the auricles interferes with the inflow of blood from the periphery and an inadequate filling of the heart results in insufficient output to maintain life When the process in the pericardium is more chronic and produces compression of the heart by fibrous tissue, the pressure within the great veins may attain very high levels Such individuals, in addition to the increased venous pressure, show enlargement of the liver with ascites No cardiac enlargement is present, although it may be suggested by an increase in the transverse diameter of the heart

From a quantitative study of the dynamics of the circulation in *constrictio cordis*, Burwell, Strayhorn and Flickinger^{12,13} have stressed the following points At rest, these individuals show a low pulse pressure, a rapid pulse rate, an elevation of the general venous pressure, a low circulatory minute volume, and a reduced stroke volume The oxygen utilization is high but the oxygen saturation of the arterial blood is normal, and there may be a normal or only slightly reduced vital capacity

Following exercise, the oxygen consumption increases but the pulse pressure and stroke volume remain unchanged The pulse rate accelerates and the circulatory minute volume increases in proportion to the rate Venous pressure increases and cyanosis is clearly visible

The exhibition of digitalis causes a slowing of the rate and a decrease in the cardiac output In brief, it appears that the only method of increasing the blood supply to the tissues is through increasing the heart rate It is not possible to increase the stroke volume, since the heart is prevented from receiving more blood during diastole

PATIENTS WITH SYMPTOMS AND SIGNS OF MULTIPLE SEROUS MEMBRANE TUBERCULOSIS

It is common knowledge that tuberculous infections of the serous membranes are very often multiple The results of the present study were confirmatory of this rule As has been related already, seven of the patients had a tuberculous pleurisy, and one had an associated tuberculosis of the peritoneum The finding of tuberculosis of the pleura or peritoneum may aid in the etiologic diagnosis of the pericardial lesion, particularly if the signs are equivocal and circulatory failure is present The case report which follows indicates the course of events in one of the cases

Case 7 An 81 year old man complained of pain in the back of three weeks' duration His family and past histories were non-contributory He regarded himself as well until a year before he was seen, when he had an infection which was called the gripe It was characterized by malaise and weakness but there was no dyspnea Since then he had had several small hemoptyses at varying intervals A

few months before he was admitted to the hospital he began to notice dyspnea and tightness across the chest on exertion, which were relieved by rest. These symptoms progressed for three weeks, then he developed an acute respiratory infection with generalized aches, pains, and prostration. For a week he had experienced attacks of paroxysmal nocturnal dyspnea accompanied by cough. There were also weakness and anorexia.

The examination revealed a temperature of 101° F, pulse rate 98 per minute, respirations 24 per minute. The blood pressure was 105 mm of mercury systolic and 75 mm of mercury diastolic. He was a pale, elderly man with some increase in the respiratory rate without distress. The examination of the head revealed nothing abnormal. The lungs showed impaired resonance and râles at the base of the left lung. The right side of the chest revealed evidence of a pleural effusion. The heart was enlarged to both the right and left, the transverse diameter being 15 centimeters. The rate was rapid and totally irregular, the sounds were very faint, and all over the lower part of the sternum there was a to-and-fro friction rub. The liver was slightly enlarged below the costal margin, otherwise the abdomen was negative. There was no edema of the legs.

Laboratory Examinations The urine was negative. The red blood cell count was 3,900,000 per cubic millimeter, hemoglobin 78 per cent (Sahli), and the white blood count was 7,400 per cubic millimeter. The Kahn reaction was negative. The non-protein nitrogen was 30 milligrams per cent, and the total protein of the blood plasma 5.2 per cent. The sputum was negative for tubercle bacilli. The pleural fluid had a specific gravity of 1.017. The cell count per cubic millimeter was as follows: red blood cells 3,810, lymphocytes 110, mononuclears 580. There was a great increase in the fibrin.

Course of Illness After three days the temperature fell to normal and finally to subnormal after several weeks. With rest and digitalis the ventricular rate was reduced. The electrocardiogram showed auricular fibrillation and low voltage. The tuberculin test in a dilution of 1:1,000 was positive. The pericardial friction rub disappeared after two weeks. The heart sounds remained distant and weak. There were rapidly recurring effusions into the right chest. He failed gradually and died after a period of nine weeks' observation.

The necropsy revealed tuberculosis of the pericardium, bilateral tuberculosis of the pleura, and pulmonary tuberculosis with a small cavity in the right lung.

There was no doubt, in this case, that the process began in the lung and then extended to the pleura and pericardium. At no time were there signs of heart or circulatory failure. It was a clear example of serous membrane tuberculosis in an elderly man.

PATIENTS WITH SYMPTOMS AND SIGNS OF A MASSIVE PERICARDIAL EFFUSION

It is universally recognized that one way in which the pericardium responds to a tuberculous infection is by the exudation of copious amounts of fluid which is frequently hemorrhagic. A pericardial effusion was found in seven of the 20 cases and varied from 700 to 3,500 cubic centimeters. All but one had fever. Three of these patients showed circulatory failure, the other four did not. It is perhaps worthy of comment that the two patients in the entire group who survived were young, with a moderate collection of pericardial fluid and no signs of cardiac compression. In one the effusion was accompanied by tuberculosis of the peritoneum, in three there was an associated tuberculosis of the pleura, and in one the disease terminated with

a miliary tuberculosis. There was nothing peculiar about the physical signs of the pericardial effusion and they were all characteristic. It does not seem unreasonable to suppose that the patients who have a poor outlook in this group are those who develop cardiac compression or an associated tuberculosis of the pleura or peritoneum. Conversely, the ones who are likely to improve are young individuals with a small effusion, without cardiac compression or signs of tuberculosis elsewhere. The following case illustrates the course of events in these cases.

A man, 70 years of age, was apparently healthy until two weeks before entry to the hospital, when he had a sudden acute pain in the left side which was severe and exaggerated by respiratory effort. Soon thereafter, shortness of breath on exertion and edema of the legs and abdomen appeared.

Examination showed a man with moderate cyanosis but without respiratory distress. The head, nose, and throat revealed nothing abnormal. The veins of the neck were greatly distended. The lungs were everywhere clear except for a number of moist rales at both bases. The heart measured 17 centimeters in its transverse diameter. The apex beat was not palpable, the sounds were feeble and distant, and there was a loud friction rub over the precordium. The liver was enlarged 6 centimeters below the costal margin, the abdomen was distended with fluid. There was massive edema of the genitalia, legs, and feet. The temperature varied from 101 to 102° F. The pulse rate varied from 90 to 100, the respiratory rate from 25 to 40 per minute.

Laboratory Examinations. The urine showed a trace of albumin and a rare hyaline cast. The pericardial fluid was serosanguinous with 6,000 red blood cells per cubic millimeter and 400 white blood cells, of which 80 per cent were lymphocytes and 20 per cent were monocytes.

Course of the Disease. During the first seven weeks of observation the temperature was elevated for five weeks, and then remained normal for two weeks. The pericardium was tapped on three occasions, and 650, 1,000 and 400 cubic centimeters withdrawn. There was temporary improvement but by the ninth week his dyspnea and edema were increasing. The veins of the neck became greatly distended. The signs over the heart remained the same but there appeared definite evidences of an effusion of fluid into the left pleural cavity. The abdomen was distended, the liver enlarged, and the edema and cyanosis were generalized. There was a pleuro-pericardial friction rub. The fluid from the left side of the chest had the same characteristics as that from the pericardium. The temperature remained normal, the pulse and respiratory rate were elevated. He failed rapidly and died three and one-half months after the onset of symptoms.

The anatomical findings were tuberculosis of the pericardium with an effusion of 550 cubic centimeters of serosanguinous fluid, tuberculous pleurisy with effusion of 900 cubic centimeters of fluid, generalized miliary tuberculosis of the lungs.

In a word, an elderly man with tuberculosis of the pericardium and a large effusion developed circulatory failure due to an increase in the general venous pressure. As the disease progressed, the left pleural cavity became involved and disseminated tuberculosis of the lung appeared as the final event. This case illustrates how a pericardial effusion may cause circulatory failure, and demonstrates the dangers of a spread to the pleura and of disseminated tuberculosis.

PATIENTS IN WHOM TUBERCULOSIS OF THE PERICARDIUM IS A TERMINAL EVENT IN THE COURSE OF ANOTHER DISEASE

There were three patients in whom tuberculosis of the pericardium was a terminal event, two had cirrhosis of the liver and one had chronic nephritis. Cardiac insufficiency was present in two, but there was no evidence that the pericardial lesion was responsible for the heart failure except in the one patient with cirrhosis of the liver. The latter case follows.

Case 14 This 55 year old man was first seen in October 1934 when he complained of anorexia, nausea, and vomiting of three weeks' duration. There had been frequent bowel movements for one week. The point of significance in his past history was the fact that he had used large amounts of alcohol for about 32 years.

The physical examination showed a man with fever which fluctuated between 99 and 101° F every day. He had lost weight but did not appear pale. The lungs were clear and the heart was not enlarged. The sounds were clear and no friction rub was heard. The peritoneal cavity was filled with fluid. There was no edema of the legs.

Laboratory Examinations The white blood count varied from 4,200 to 15,000 per cubic millimeter. The ascitic fluid on two occasions had the characteristics of a transudate, a specific gravity of 1.003, white blood count of 108 per cubic millimeter and red blood count of 372 per cubic millimeter. Roentgen-ray of the chest showed that the lungs were clear and the heart not enlarged. An electrocardiogram revealed left ventricular preponderance and auricular fibrillation.

Course of the Disease Four weeks after he was first seen, he commenced to have shortness of breath, increasing anorexia, and edema of the legs and abdomen. He was slightly jaundiced and râles appeared at the lung bases. The heart reverted to a normal sinus rhythm with a partial heart block. The edema progressed and he died two weeks later.

The necropsy findings were tuberculosis of pericardium, alcoholic cirrhosis of the liver, chronic duodenal ulcer, ascites.

In this case, the tuberculosis of the pericardium was a terminal event in a patient with cirrhosis of the liver. The cirrhosis was outstanding.

PATIENTS IN WHOM TUBERCULOSIS OF THE PERICARDIUM IS FOLLOWED BY MILIARY TUBERCULOSIS

Disseminated tuberculosis following tuberculous infection of the pericardium is not infrequent. It was present in five of our cases. The cases in which the pericardium was involved as a part of a disseminated infection were, of course, not included in this study since they gave no evidence of pericardial disease during life. Others have commented on the frequency with which tuberculosis of the pericardium is followed by dissemination of the disease and this sequence undoubtedly is responsible in part for the high mortality. In some cases the whole course of the disease is afebrile and the finding of miliary tubercles everywhere comes as a complete surprise.

COMMENT

Taking the evidence as a whole, the clinical features of tuberculosis of the pericardium may be reviewed as follows. The diagnosis should be entertained, especially in elderly individuals, when there are symptoms and signs of an infection with localizing signs indicating a lesion of the pericardium. There may be only a pericardial friction rub of short duration, or unmistakable evidence of a pericardial effusion, and of cardiac compression with peripheral venous stasis and edema. It perhaps should be emphasized that in some patients the signs of infection predominate and the evidence for a lesion of the pericardium is very meager. It may consist only of a feeble apex impulse and distant heart sounds, signs which, in themselves, are certainly not always compatible with disease of the pericardium. It is also worthy of comment to say that there may be the signs of "inflow stasis" or peripheral edema indicating pericardial disease without signs of an acute infection.

If the process spreads from the pericardium to the pleura or if there are signs of tuberculosis of the peritoneum or the lungs at the same time, then the diagnosis is much simpler. Finally, one should remember that miliary tuberculosis in the elderly may begin as tuberculosis of the pericardium.

Differential Diagnosis In my experience, the diseases with which tuberculosis of the pericardium have been confused most often are (1) coronary artery disease with consequent heart failure, (2) cirrhosis of the liver, (3) rheumatic pericarditis.

Coronary Artery Disease In elderly individuals who complain of constriction in the chest and symptoms suggesting cardiac insufficiency without evidence of valvular disease or hypertension, the diagnosis of coronary artery disease is most often entertained. If this is accompanied by precordial pain that is followed by fever and a pericardial friction rub, the temptation to make the diagnosis of a coronary occlusion with myocardial infarction is great. Even in the absence of a friction rub, the signs over the heart may be similar in the two conditions under discussion, that is, the heart sounds are distant and the apex impulse feeble. This is particularly true of patients with coronary occlusion who have developed an aneurysm of the left ventricle following infarction. One point of difference may be helpful in these cases. The impulse after coronary occlusion is more likely to be well felt but the heart sounds are feeble and there is often a gallop rhythm present, whereas in pericardial disease, the apex impulse and the sounds are both distant. In addition, the roentgen-ray diagnosis of an aneurysm of the left ventricle may aid in the differentiation.¹⁴ The electrocardiogram may be helpful but it is not always decisive since changes in the T-waves similar to those occurring in coronary occlusion are reported in cases of pericardial disease. The differentiation must be made largely on the basis of the clinical course of the disease, a careful analysis of the history, and the various physical and other findings.

Cirrhosis of the Liver Inasmuch as two of the cases described had an

alcoholic cirrhosis of the liver and a terminal tuberculosis of the pericardium, both conditions may coexist in the same individual. In the one case, the cirrhosis was limited in extent and therefore latent. In the other, the symptoms and signs were predominantly those of cirrhosis, and the diagnosis of tuberculosis of the pericardium was latent and disclosed by the pathologist.

The instances in which tuberculosis of the pericardium is likely to be confused with cirrhosis of the liver are those in which there is an insidious onset with progressive signs of stasis, and ascites which is disproportionate to the other evidences of increased venous pressure. This is the picture that is seen most often in *concretio cordis* with or without calcification of the pericardium, and it is not seen so often in the more acute type which has been described in this paper.

It is convenient at this point to say something about so-called "cardiac cirrhosis," since this is the condition seen as a result of repeated attacks of heart failure and chronic venous stasis. It should be clearly distinguished from other types of hepatic cirrhosis, since it is highly doubtful whether the alterations in the structure of the liver in chronic stasis are of sufficient degree to cause portal obstruction. It consists of a central necrosis, usually of the hemorrhagic type. The necrotic cells are removed by macrophages and, if no regeneration takes place, the stroma of the liver gradually contracts, resulting in areas of sclerosis around the central veins. As a result of this process the liver is diminished in size and its surface finely and evenly granular. It is to a liver at this stage that the name "cardiac cirrhosis" has been given.

In a certain number of cases, perhaps due to a stimulus of an unusually extensive central necrosis or repeated attacks of congestion, very active regeneration of liver cells takes place. If these areas of regeneration surround the sublobular veins, they tend to be roughly circular in outline. If they follow the radicles of the portal vein, they have a curious branching arrangement which has been likened to a fern leaf. When Youmans and Merrill¹⁵ collected and reported the cases of pericarditis calculosa several years ago, they called attention to the fact that at least one-third of the reported cases were associated with an "atrophic" cirrhosis of the liver. They were not of the opinion that the cirrhosis of the liver in these cases resulted from chronic venous stasis, but that it was a further expression of the fundamental disease process which, in most cases, was tuberculosis. Without more details of the histologic changes in the liver being available, it is impossible to say whether the changes observed in the liver in cases of pericarditis calculosa are the result of chronic stasis or not.

One of the most reliable tests for discriminating between cirrhosis of the liver and "inflow stasis" is the general elevation of venous pressure. That is to say, the venous pressure is increased in both the veins of the upper and lower extremities in pericardial disease, whereas in cirrhosis of the liver the venous pressure of the legs may be increased in the presence of ascites but

the pressure in the veins of the arms is normal or only slightly elevated. The presence of other signs of portal obstruction is often more conspicuous in cirrhosis of the liver. It is perhaps worthy of comment that patients with limited cirrhosis of the liver may die of heart failure, as in the cases reported by McCartney.²¹ This was true in 25 per cent of the cases. In most of the cases the cirrhosis of the liver played no part in the clinical picture.

One may sum up the discussion by saying that patients with latent or advanced cirrhosis of the liver may develop tuberculosis of the pericardium as a terminal event. It is also recognized that venous stasis resulting from pericardial disease may produce secondary anatomical changes in the liver. The relative importance of these changes in the production of ascites cannot be assessed at present. Certainly, recurrent ascites is observed without any change in the liver other than chronic passive congestion. Finally, it is not uncommon for patients with latent cirrhosis of the liver to die as a result of independent heart disease. The cases in which confusion most often arises are those with recurrent ascites and an increase in general venous pressure. The last feature is of the highest importance in differential diagnosis.

Rheumatic Heart Disease The appearance of tuberculosis of the pericardium in the younger age groups requires differentiation from rheumatic heart disease. In some this is not difficult, especially if there is an associated arthritis or if there are signs of valvular disease, or changes in conduction by electrocardiographic examination. When tubercle bacilli can be obtained from the pericardial fluid or when tuberculosis exists elsewhere then the diagnosis is less difficult. However, when the fluid fails to contain demonstrable tubercle bacilli it is not possible to make the discrimination on the basis of the characteristics of the fluid alone. They both have the characteristics of an exudate, contain large amounts of fibrin and an increase in cells, and both of them may be hemorrhagic. In a few, the diagnosis can be made only from a study of the course of the disease. I have seen several patients who had been sent to tuberculosis sanatoria on account of pleurisy and pericarditis with a hemorrhagic fluid who returned after two years with unequivocal signs of mitral stenosis. This was excellent testimony that the original disease was rheumatic fever.

It is perhaps well to recall that while disturbances in rhythm or conduction are not common in tuberculosis of the pericardium, they have been observed, so that this sign alone does not favor the diagnosis of rheumatic heart disease. It has been suggested by Bellet, Gouley, and McMillan that the presence of arrhythmias may suggest tuberculous disease of the heart muscle, especially of the right auricle.

Speaking broadly, the diagnosis of rheumatic pericarditis may not be difficult in most cases, in the few in which tuberculosis is suspected, the various points mentioned above should prove helpful.

PROGNOSIS AND TREATMENT

From the study of these cases and others reported, it is difficult to escape the conclusion that tuberculosis of the pericardium is a most serious disease. The reasons would appear to be the age at which it is common, the tendency to multiple serous sac infection or disseminated tuberculosis, and the fact that the location of the lesion interferes with the functions of the circulation. That some patients recover and survive a number of years without difficulty, there seems to be little question. But even when there is healing of the pericardial lesion the end result may be cardiac compression resulting from the constriction of the heart by fibrous tissue with or without calcification.

Within recent years, striking advances have been made in the surgical treatment of *concretio cordis*^{10, 11, 13, 16, 17}. The best results have been obtained in relatively young individuals who have a fibrous pericardium without signs of an active infection. In the cases of *concretio cordis* in which active tuberculosis has been found at the time of operation, the results have been unsatisfactory. Although the reported experience with surgical treatment is limited, it would seem justified to say that operation in the face of an active infection has little to offer.

Another method that has been used is the injection of air or oxygen into the pericardial cavity following the aspiration of fluid^{18, 19}. The purpose of this is to prevent the development of adhesions. The only case in which I have seen this method used resulted in failure and the patient died.

There is no doubt that the pericardium should be tapped in the patients who show signs of cardiac compression, provided the compression is due to a pericardial effusion and not a fibrous exudate. A falling systolic pressure, a rising venous pressure, and clinical signs of venous stasis are indications for pericardial tapping.

SUMMARY AND CONCLUSIONS

From a study of 20 cases of tuberculosis of the pericardium, the following conclusions are justified:

1. Tuberculosis of the pericardium is seen most often in patients over 40 years of age, and it is essentially a disease of the elderly.
2. Patients frequently present themselves with
 - a. Symptoms and signs of a wasting disease and obscure fever
 - b. Edema and congestion simulating cardiac insufficiency
 - c. Multiple serous membrane infections
 - d. Miliary tuberculosis
3. It may occur as a terminal event during the course of another disease.
4. The diagnosis may be entertained when there are
 - a. Symptoms and signs of an infection
 - b. Localizing signs over the pericardium, such as—

- (1) Pericardial friction rub
- (2) Pericardial effusion
- (3) Signs of thickening of the pericardium
- c Signs of circulatory failure which is predominantly of the "inflow stasis" type
- d Signs of extension of the process to the other serous sacs, or a disseminated tuberculosis
- 5 It may be confused with
 - a Coronary artery disease
 - b Cirrhosis of the liver
 - c Rheumatic pancarditis
- 6 Tuberculosis of the pericardium arises from an invasion of tubercle bacilli from the mediastinal lymph nodes, the lungs, the pleura, or peritoneum
- 7 The prognosis is always serious, and present methods of treatment are unsatisfactory

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FULMINATING SEPTICEMIA ASSOCIATED WITH PURPURA AND BILATERAL ADRENAL HEM- ORRHAGE (WATERHOUSE-FRIDERICHSEN SYNDROME); REPORT OF TWO CASES WITH REVIEW OF THE LITERATURE

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THE occurrence of adrenal hemorrhages of varying degree is a matter of common clinical and pathological knowledge in such conditions as diphtheria, scarlet fever, measles, and pneumonia. In new-born and still-born infants, adrenal hemorrhage, likewise, is known to occur and is chiefly of mechanical or traumatic origin. Snelling and Erb¹ found 43 cases of adrenal hemorrhage in 3,637 consecutive autopsies, an incidence of 1.19 per cent. Of these, 15 occurred in the new-born. In older children, adrenal hemorrhage is usually of toxic or infectious etiology.

The association of fulminating purpura with bilateral adrenal hemorrhage has long been recognized. The earliest case reports of this condition are to be found in the English literature. Garrod and Driysdale,² Voelcker,³ Still,⁴ Batten,⁵ Talbot,⁶ Blaher and Bailey,⁶ were among the first to note this association, but it remained for Graham Little,⁹ writing in 1901, to recognize and classify such cases as a distinct clinical entity. Waterhouse,¹⁰ in 1911, reported one case and collected 15 from the literature. He attempted to portray a definitive disease picture, but added no knowledge as to the etiology beyond observations concerning a possible bacterial cause, which even earlier observers had suggested. Friderichsen,¹¹ in 1918, in an inclusive review, brought the literature up to date. His clinicopathological picture was quite complete, but he, likewise, added no new information concerning etiology. McLagan and Cooke,¹² in 1916, were perhaps the first to incriminate the meningococcus in two case reports, which fit definitely into the so-called Waterhouse-Friderichsen picture. Since that time there have been several other reports, chiefly in the German literature, notably those by Baumann, 1931,¹³ Glanzmann, 1933,¹⁴ and Bamatter, 1934.¹⁵ The literature is brought up to date by Aegerter¹⁶ in a recent excellent review. He has collected 55 case reports which fit into the clinical picture of this syndrome and in addition presents two of his own. To these may be added three cases presented in a study of meningococcemias by McLean and Caffey¹⁷, another reported by Glanzmann¹⁴ and two cases in a series of suprarenal hemorrhages studied by Snelling and Erb.¹ Foucar²⁶ in a recent report adds still another case which presents a typical Waterhouse-Friderichsen picture.

The sequence of events occurs with sufficient regularity to enable one to

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paint a picture which stamps this syndrome as a clinical entity. The majority of cases occur in young children. In the reported cases the ages varied from two months to nine years with only seven, or approximately 10 per cent, occurring in adults. Forty-five, or 70 per cent, occurred in infants two years or younger. Sex apparently plays no part since the cases occurred with equal regularity in males and females.

The case history, characteristically, tells of a previously healthy child who quite suddenly becomes ill. The early symptoms are non-specific and are such as may occur in any acute infection. Many of the histories state that the child, having gone to sleep, apparently quite well, awakens suddenly during the night with a cry. Vomiting occurs early and frequently but is moderate, and the character of the vomitus is not notable. Hyperpyrexia is present and most cases report a septic type of fever with the upper levels as high as 108° F. Chills occur, but are present infrequently. Diarrhea and abdominal pain, never localized, are, likewise, present occasionally. Central nervous system symptoms appear early and vary from severe headache, in adults, to delirium, restlessness and generalized convulsions in children. The patients soon lapse into a lethargic, stuporous state and remain so until exitus occurs.

Within a few hours after onset a striking cyanosis is noted. This is mentioned in 29 case reports, or 46 per cent, and in two others a peculiar alternation of pallor and cyanosis is reported. The cyanosis is quite out of proportion to the degree of pulmonary involvement, but together with the tachypnea and dilatation of the alae nasae, it has often led to an erroneous diagnosis of pneumonia.

Soon after the appearance of cyanosis a petechial eruption is noted, involving the face, neck, trunk and extremities. The petechiae are bluish-red in color, irregularly shaped, and do not fade on pressure. The conjunctivae often present similar petechiae. They appear quite suddenly and soon become associated with a diffuse, macular, purpuric rash. This latter frequently tends to become confluent and form areas often as large as the palm of one's hand. The skin, thus, has a mottled, livid appearance, not at all unlike postmortem lividity. This rash persists until death occurs.

Examination of the patient reveals an extremely toxic, often comatose child, breathing rapidly and shallowly. The respirations occasionally change in character and become stertorous and of a Cheyne-Stokes variety terminally. At the onset of the illness, the pulse is proportionate to the hyperpyrexia, but later it becomes running, feeble and thready. Physical examination of the chest may reveal moist râles, posteriorly, at the bases. There is no change in cardiac contour, nor does auscultation reveal any changes beyond a sinus tachycardia and enfeeblement of the heart sounds. The abdomen is negative to examination. The extremities reveal only the characteristic rash described above. There are no characteristic neurological findings. Headache may be present and is often quite severe in

adults Cervical rigidity is usually absent, or there may be the faintest suggestion of meningismus present The reflexes are unaltered as a rule

These dramatic events run their course in from 24 to 48 hours The majority of cases terminate in 24 hours or less Other less frequent findings are mentioned in occasional reports, such as a disparity between the high oral and rectal temperatures and a low surface temperature, tremors of the extremities and muscle flaccidity, all as variants from the usual picture

The laboratory offers little help in diagnosis aside from the possibility of finding meningococci in blood smears from purpuric areas as suggested by McLean and Caffey,¹⁷ Netter, Salanier and Wolfrom¹⁸ The former workers were able to demonstrate intracellular gram-negative organisms in smears from the skin lesions in 83 per cent of a series of cases of meningococcus meningitis

Because of the fulminating character of the disease there are few detailed reports of the blood picture There is usually a leukocytosis Varying figures are given from 7,000 to 88,500, the average being about 12,000 There is a definite increase in granulocytes with a shift to the left Three reports mention platelet counts Battley¹⁹ 216,000, Glanzmann mentions a thrombopenia but gives no figure, Bamatter, 172,000 Generalizations cannot be made from these three figures, but in view of the subcutaneous vascular lesions it appears that an adequate explanation of the purpura is at hand without calling upon a thrombocytopenia

Spinal fluid examination usually reveals a clear, colorless fluid with perhaps a slight increase in cells, usually polymorphonuclears Various other constituents of the fluid, such as globulin and sugar, show no change Aegerter notes that of all the patients who were tapped only six showed abnormalities In three there was an increase in cells, in six the meningococcus was isolated, and in four an increase in pressure was present

PATHOLOGY

The outstanding pathological finding is a massive, bilateral adrenal hemorrhage This was present in approximately 95 per cent of the cases Occasionally only one adrenal is involved and when so, it is usually the right The hemorrhage may vary from multiple, pin point areas to a massive type, converting the adrenal into a "blood cyst" Almost always it is confined within the limits of the capsule of the gland In only one of the reported cases was rupture noted to have occurred with a resultant hemorrhagic peritonitis

The histopathology of the adrenals usually merely confirms the gross findings The densest hemorrhage appears to be in the region of the medulla and zona reticularis of the cortex It apparently involves the other layers by diffusion and often leaves a narrow layer of cortical tissue in the zona glomerulosa intact Thrombosis or embolism is rarely seen and an inflammatory reaction is usually absent

The skin lesion is apparently due to direct involvement of capillaries and arterioles by the causative organism. Brown²⁰ found an inflammatory reaction in the capillaries and arterioles of the subcutaneous tissue and corium with a perivascular leukocytic infiltration, in cases of meningococcus septicemia. Injury to vessel walls allows an escape of red cells, thus accounting for the purpuric eruption.

Examination of the brain reveals only a congestion of the superficial vessels of the leptomeninges. This is true even in the cases of definitely proved meningococcal etiology.

Other pathological findings are merely such as would occur with an acute infection. Namely, Cloudy swelling of the parenchymatous viscera, acute splenic tumor and often a terminal pulmonary edema and congestion. A finding of perhaps more importance is the frequent occurrence of an enlarged thymus, prominence of the mesenteric lymph nodes, hyperplasia of Peyer's patches and solitary lymphoid follicles of the intestines. Sixteen cases in the literature were reported to have enlargement of Peyer's patches and lymph nodes. Ten specifically mention enlargement of the thymus. This thymolymphatic prominence has been pointed out by Rabinowitz²¹ and Bamatter¹⁵. The latter, in fact, believes it to be a factor of some importance in the pathogenesis of this disease, in view of recent work showing a definite correlation between status thymolymphaticus and adrenal hypoplasia.

ETIOLOGY

The determination of etiology presented difficulty to the early observers of this syndrome, perhaps because of its inherently fulminant character. Bacterial infection was early indicated as the probable cause, but a variety of organisms was found. Dudgeon²² found a *Staphylococcus aureus* in one case and a pneumococcus in another. Graham Little was able to demonstrate streptococci in sections of the skin. Waterhouse's case yielded a negative postmortem spinal fluid and blood culture, and he reported that in most cases cultures had been sterile. It is interesting to note that at the time of Friderichsen's report only 12 cases included data on blood culture. Of these, seven were sterile and the others included the variety of organisms mentioned above. McLagan and Cooke's¹² work, already referred to, is the first report to incriminate, definitely, the meningococcus. Herrick²³ has emphasized the fact that it is in the fulminating type of meningococcal infection that a striking purpura is most apt to be found. It is, moreover, in this type of case that adrenal hemorrhage is seen, rather than in the usual manifestations of meningococcus infection. It may be argued that the involvement of the skin and adrenal medulla, both of similar ectodermal origin, is an evidence of the ectodermal tropism of the meningococcus. The pneumococcus, likewise, possesses an ectodermal or epithelial tropism and, moreover, is capable of producing purpuric skin lesions as demonstrated by Mair²⁴ and Julianelle and Reimann²⁵.

Since McLagan and Cooke's report 21 cases, in the data of which definite statements as to etiology are included, have been added to the literature. Of these, 12, or 60 per cent, were due to meningococci. The others, constituting 40 per cent, either gave sterile cultures or growths of *Streptococcus hemolyticus* were obtained (Snelling and Erb). It is interesting to note that Bamatter, in 1934, found that only four bacteriological examinations had been done ante-mortem. Since then, three additional ante-mortem investigations have yielded meningococci. It seems, then, that the meningococcus is the most frequent, but not the only etiological agent found in this condition.

I should like to add to the total of 64 reported cases, two which recently occurred at the University Hospital.

CASE REPORTS

Case 1 C. H., white, female child, aged four years, admitted to the Pediatric service at the University Hospital on April 6, 1936, with a complaint of pain in the side, chills and vomiting. The past and family histories are completely non-contributory. The child had been entirely healthy until onset of the present illness. Two days prior to admission the child's mother had noticed a slight cough. On April 5, 1936, one day prior to admission, there was a slight nasal mucoid discharge. The child went to bed at 8 00 p.m. after having eaten a light supper and appeared quite well. At 11 00 p.m. she suddenly awakened with a cry and complained of pain on the right side of the chest. Soon afterward she experienced a chill, and vomiting occurred. The child remained restless, feverish and disoriented throughout the night. At 6 40 a.m. there was a generalized convulsion which lasted about five minutes. She was seen by a physician who advised immediate hospitalization. On the way to the hospital another convulsion occurred.

When seen in the hospital the child appeared extremely toxic, temperature 104° F., respirations rapid and shallow, and pulse averaging 165 to 180 per minute, characterized as thready and of poor volume. At this time over the chest could be seen numerous purpuric spots, limited to the right side and apparently distributed along the intercostal spaces. The child was lethargic, but her attention could be attracted. On physical examination the following important findings were noted: Several petechial hemorrhages in the conjunctivae, dilatation of the alae nasi with respiration, injection of the pharynx and fauces. Examination of the chest revealed it to be resonant, but on auscultation the breath sounds were broncho-vesicular and there were fairly numerous moist and crepitant râles at the bases, posteriorly. Aside from the tachycardia and feebleness of the pulse, the cardiovascular system was negative. The abdomen was distended, but showed no other changes. The reflexes were present and in the case of the patellar were even hyperactive. No cervical rigidity or other signs of meningeal irritation were present.

The blood picture, on admission, showed 3,000,000 red blood cells, hgb. 80 per cent, a total white count of 7,000 with 80 per cent polymorphonuclears and 20 per cent lymphocytes. Spinal fluid examination revealed a clear, colorless fluid containing 26 cells per cu. mm., predominantly polymorphonuclears. Blood culture, immediately after admission, showed a profuse growth of *Neisseria intracellularis*. Agglutination with polyvalent anti-meningococcus serum was markedly positive up to a dilution of 1:1560.

The child was put to bed immediately after admission and intranasal oxygen was started. In spite of sponges the temperature rose to 107.6° F. At the height of the

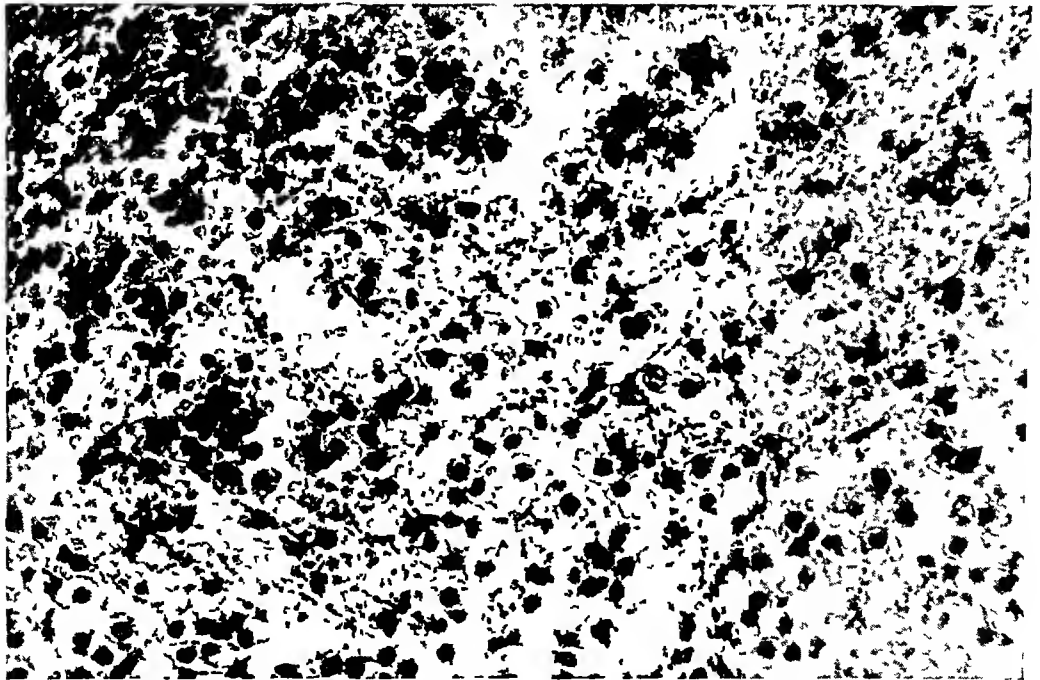
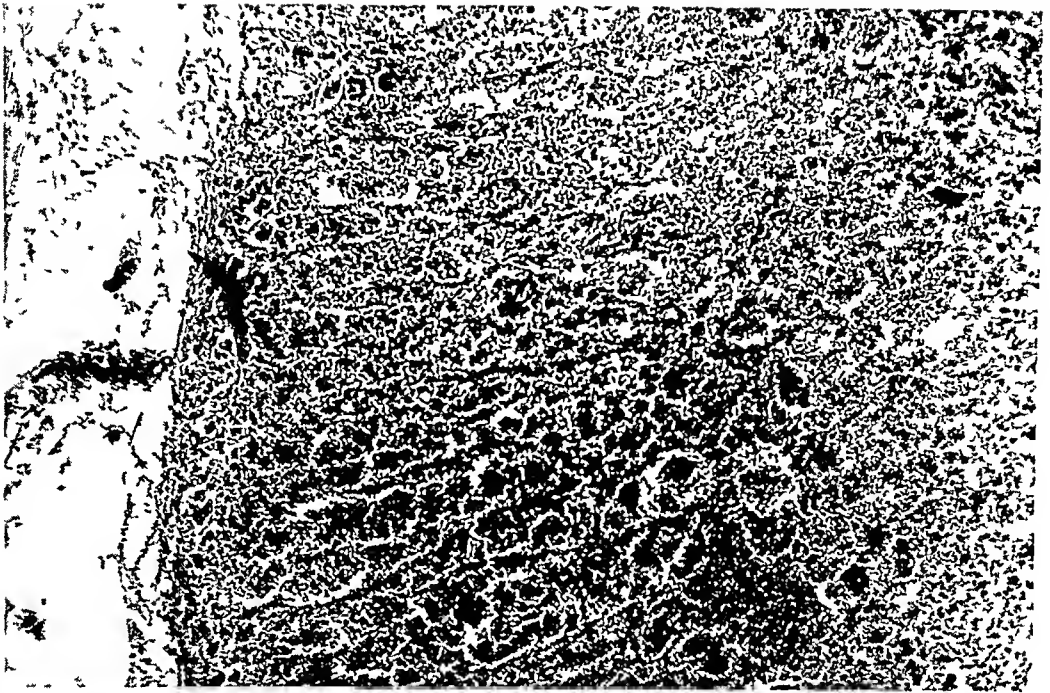


FIG 1 Low and high power photomicrographs of the adrenal (case 1), showing extensive hemorrhage and destruction of parenchyma

fever a macular, purpuric eruption appeared on the face, neck and lower extremities. Cyanosis of the hands, feet and back was quite pronounced. Respirations became slower and more labored. About one-half hour before death the child vomited about 200 c.c. of liquid black material, which gave a positive chemical reaction for blood. In spite of all medications death occurred at 5 30 p.m., April 6, 1936, approximately 18½ hours after onset.

An autopsy was performed two hours following death. The body was that of a well-developed and well-nourished child, showing a macular, petechial and purpuric eruption, most marked over the anterior chest. Numerous petechiae were seen in the bulbar conjunctivae. The mesenteric lymph nodes were prominent and had a reddish tint. The thymus was of normal size and presented no gross pathologic change. The lungs, liver, kidneys, heart, pancreas and gastrointestinal tract revealed no gross or microscopic lesions. The spleen was moderately enlarged and weighed 60 gm. The adrenals were of the usual size, but had a striking, deep, hemorrhagic color. On section gross hemorrhagic involvement of the cortex and medulla was present. Histological examination revealed diffuse hemorrhage throughout the entire adrenal substance with beginning necrosis of both the medullary and cortical tissue. Examination of the brain revealed congestion of the vessels of the leptomeninges, but no other gross or histological changes.

Case 2 The history and physical examination of this case are necessarily fragmentary since the child was brought to the accident room in a moribund condition and died within a few minutes after admission. The brief anamnesis was all that could be obtained from a distraught and hysterical parent. This is a white, female child, R. C., aged 2½ years, who became ill quite suddenly during the evening of July 7, 1936. Her illness was characterized by marked prostration, hyperpyrexia and several generalized convulsions. The patient was seen by a physician on the morning of July 8, 1936, at which time she was comatose. The skin of the face, neck, trunk and extremities was covered by a profuse, macular, petechial and purpuric eruption, which, in some places, was confluent. The individual lesions measured up to approximately 5 cm. in diameter. Immediate steps were taken to secure hospitalization, but as stated above, the patient was in a moribund state when first seen in the accident room. Death occurred at 2 00 p.m., July 8, 1936. The duration of illness, as closely as can be determined, was less than 24 hours.

An autopsy was performed one hour after death. External examination revealed a diffuse, macular and, in some places, petechial eruption, involving the face, neck, back, abdomen, chest and the upper and lower extremities. Although only slight rigor mortis was present and only a short time had elapsed since death one was struck by the diffuse cyanotic discoloration of skin, apart from the distinct eruption. The conjunctivae were injected, but presented no petechiae, nor were petechiae seen on any of the serous membranes of the body. There was moderate gaseous distention of the intestinal tract. The thymus was somewhat enlarged, weighing 30 gm., and there was prominence of the mesenteric lymph nodes which appeared somewhat reddened. Lymphoid hyperplasia was, likewise, noted in the Peyer's patches and solitary follicles of the ileum. The lungs, grossly and histologically, revealed evidence of edema and congestion. The heart, liver and kidneys showed no marked lesions aside from a moderate degree of cloudy swelling, compatible with any acute infection. The spleen was enlarged, weighing 65 gm. and histologically showed a typical acute splenic tumor. The adrenals, although of normal size and shape, exhibited a diffuse, deep red, hemorrhagic appearance, which completely obliterated all normal landmarks of cortex and medulla. Histologically there was extensive hemorrhage confined within the limits of the capsule of the adrenal. The densest collection involved the medulla and zona reticularis with apparently secondary involvement of the outer layers of the cortex. There was complete disruption and necrosis of all but a very

small outer shell of adrenaal tissue. In addition to fresh blood, collections of blood pigment could be seen scattered throughout the section. A careful search for organisms was made in sections stained by Goodpasture's method, but none were found.

The brain was examined by Dr. James G. Arnold, Jr., who found scattered petechial hemorrhages present, particularly in the region of the ventricular system. One early encephalitic focus was found in the thalamus. There was nothing specific in the findings to suggest a purulent meningitis, they were simply such as might be present in any septicemia.

Blood Culture postmortem blood culture revealed a pneumococcus, type 1

COMMENT

In view of the predominant meningococcal etiology, the infrequency with which these cases are seen is surprising. It appears to us, and to several other observers, notably Rabinowitz, Bamatter and Aegerter, that the thymolymphatic prominence is an important factor in the pathogenesis of this disease. To the 10 reports of thymic enlargement we add, in case 2, additional support in the form of a thymus, weighing 30 gm., in a 2½ year old child. The definite relationship between atrophy, or hypoplasia, of the adrenals and status thymolymphaticus is a well known fact. The assumption that the rarity of these cases is the result of the infrequent coincidence of these two factors can be proved only by further careful observations. Other constitutional and physiological factors have been mentioned, such as the marked vascularity of the adrenals in infants and the increased sensitivity of the suprarenal vessels to vasodilating toxins, but they seem untenable in view of the occurrence of cases in adults.

It is interesting to note, here, that even in cases of definitely proved meningococcal etiology, the leptomeninges have shown only slight involvement in the form of capillary congestion. This, of course, merely supports the well known occurrence of bacteremia preceding the usual manifestations of meningitis.

A hitherto unmentioned pathological finding is noted, also, in case 2, i. e., the occurrence of minute petechial hemorrhages in the white substance of the cerebral hemispheres, especially adjacent to the ventricular system. This, however, is believed to be nonspecific and merely in keeping with the finding of subserosal petechiae in the epicardium, pleura and peritoneum in this and other types of septicemia. It may, however, be of significance as the background for the coma and convulsions often seen in these cases.

The frequency of sterile blood cultures, even in recent reports, is deserving of consideration. Bamatter suggests as possible reasons phagocytosis by body cells, antibodies in the serum being carried over into the culture media, the organisms, though few in number, being especially virulent in their effect. Finally, the isolation of other organisms, such as the pneumococcus in one of our cases, necessitates some explanation. One may suggest an ectodermal tropism, similar in a way to that of the meningococcus, on the part of pneumococci.

SUMMARY

1 Two cases of the so-called Waterhouse-Friderichsen syndrome are reported

2 Review of the literature reveals a total of 64 cases, 70 per cent occurring in children below the age of two years

3 Twenty-one case reports mentioned bacteriological etiology, 60 per cent were meningococcal in origin. The remaining 40 per cent were due either to *Streptococcus hemolyticus* or the pneumococcus, or were reported sterile after careful examination

4 The outstanding pathological finding is bilateral adrenal hemorrhage, usually of a massive type

5 The clinical picture of a rapidly fulminating, septic course, associated with a striking purpura, is considered of sufficient definiteness to warrant consideration of this syndrome as a clinical entity

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VARIATIONS IN RESPONSE TO THERAPY IN PERNICIOUS ANEMIA *

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ADEQUATE treatment of pernicious anemia should result in the restoration of a normal blood picture and in the disappearance of those symptoms and signs which are not due to irreversible tissue changes. It is necessary to know the amount of potent factor required to bring the erythrocytes to normal and to maintain these cells at such a level. It is also important to determine whether, in spite of apparently adequate therapy, a significant fall in the red blood cell count may occur. If such a fall occurs we should like to know whether it is attended by other evidence of clinical relapse. A study of the records of the patients under active treatment in the Hematology Clinic of the New York Hospital was undertaken to see if information could be obtained which would throw some light upon these problems.

The total series of patients studied numbered 36, of this total, 33 patients had been given treatment for a sufficient period of time to elevate the red blood count to normal, and of these, 32 had been treated in the Clinic for periods of time that permit a satisfactory evaluation of data which might yield information about maintenance conditions. Of the group of 32 patients the average length of the maintenance period was 21 months, the shortest period being five, the longest 50 months. The preparations used in treatment were Lederle Liver Extract (3 c c of which were derived from 100 grams of liver), and an unconcentrated extract prepared in the laboratories of the New York Hospital, 10 c c of which were derived from 50 grams of liver. The latter preparation was given those patients who could not afford the cost of the commercial preparation. The amount of New York Hospital extract given was shown by experience to produce results comparable to those obtained by the highly refined commercial preparation. These preparations were given by intramuscular injection, the average amount consisting of a total monthly dose of material derived from 300 grams (Lederle) or from 200 grams (New York Hospital). The patients were seen in the Clinic at least once a month when counts were made and the patients questioned and examined. When the red blood cell count fell appreciably or the patient showed some subjective or objective evidence of relapse the amount of material was increased or was supplemented by whole liver or by Lextron †. As these patients were observed on their recurring visits, the impression was gained that the amount of liver given routinely

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† LEXTRON (Eli Lilly)-Liver Stomach Concentrate 0.455 gm, Ammonium Citrate (Green) 0.2 gm Adsorbed Vitamin B—0.016 gm

was yielding satisfactory results in most cases, and the counts (both individually and as regards the general trend) seemed up to the normal standards

A standard for erythrocyte values has been established from numerous studies of normal individuals. Wintrobe¹ has published an analysis of a number of such series from the literature as a result of which the average red blood cell values for men have been placed at 5.4 and for women at 4.8 million erythrocytes per cubic millimeter of blood. In his own series of normals (86 men and 101 women) the normal variation for men was found to lie between 4.9 and 5.98, and for women, between 4.44 and 5.60. In our pernicious anemia patients who were in remission the average count for the entire group of women (19) was 4.5 and for men (13) 4.83. It will be noted that these figures fall below the mean average of the normal group but lie within the limits of normal variation for women and just under the low normal for men. These averages are lowered by inclusion of several cases not satisfactorily controlled. If we consider the mean erythrocyte count of 4.44, given by Wintrobe, as the lower limit of normal variation for women, there were five patients in this group whose average counts lay below this figure, and of the men also five patients whose average remained below the lower figure for men. These patients are presented as cases 1, 21, 31, 23 and 36 (women) and 24, 14, 9, 12 and 25 (men). The lowest average in this group occurred in two women both with counts of 3.9, and of the men, two patients had average counts of 4.3. If these 10 cases are excluded from the series—the 10 records will be later presented in detail—it will be seen that the remaining 23 patients show erythrocyte averages that lie well within the range of normal values and they can be considered well controlled from a hematologic standpoint. Since these patients (70 per cent of the series) gave a satisfactory hematologic response to amounts of active principle which consisted on the average of potent factor derived from 300 grams of liver (Lederle) or from 200 grams (New York Hospital Extract) per month, they may be used for comparison with those subjects whose average counts failed to attain the normal. It will be of interest to compare the amount of active principle given to these latter individuals with the average used for the entire group and to see whether the disease under these presumably unfavorable conditions seemed to be clinically controlled or showed some evidence of activity.

CASES REFRACTORY TO TREATMENT AS DEMONSTRATED BY LOW RED BLOOD CELL COUNTS

As previously stated, the average total dose of material per month consisted of substance derived from 300 grams of liver (Lederle) or from 200 grams (New York Hospital). This quantity undoubtedly exceeds the minimum requirement for the average case. Murphy² was able to maintain a normal erythrocyte level, of from 4.5 to 5 million or over, with as little as 1 c.c. prepared from 100 grams (Lederle) given at intervals of about 21

days, and Stungis² with an average monthly total quantity of material from 80 grams (preparation not stated). It will be noted, therefore, that although amounts considerably in excess of that usually found effective were given, the average count of these patients fell below the optimal level. A brief summary of this group of "refractory" patients is presented to emphasize the amount of liver extract used, the hematologic response to treatment and the symptomatology as it appeared at the end of the maintenance period arbitrarily chosen for the purpose of the study.

Case 1 A woman, 40 years of age, gave a history of periods of exhaustion, glossitis and diarrhea with intermittent paresthesias of the hands and feet for five years. The erythrocyte count on admission was 148 million. The maximum reticulocyte response was 19 per cent on the sixth day, and the erythrocytes reached 46 million in the third month of treatment. This level was not held, and an average count of 39 million was maintained over a period of 23 months. During this time she received as an average total monthly intake, the material derived from 600 grams (Lederle extract) alternating with that from 200 grams (New York Hospital extract). Her general and neurological symptoms were entirely controlled, and there was no objective evidence of progress of the disease. She experienced periods of nervous irritability and stated that she would fly into a rage with little provocation. She would awaken at night obsessed with fear of she "knew not what."

Comment Except for periods of emotional instability this patient was free of symptoms.

Case 23 A woman, aged 30 years, with symptoms of vertigo and weakness for two months, showed an erythrocyte count on admission of 20 million. A reticulocyte peak of 14.9 per cent occurred on the fourth day of treatment, and an erythrocyte count of 45 million was obtained in five weeks with a total dose consisting of the material derived from 500 grams of liver (Lederle extract). The average amount of material given per month over a period of 15 months was that derived from 300 to 600 grams (Lederle extract) and the average erythrocyte level attained during this time was 42 million red blood cells. This patient also had exophthalmic goiter for which a subtotal thyroidectomy was done during her treatment for pernicious anemia.

Comment The general symptoms have disappeared and there has been no evidence of central nervous system involvement.

Case 31 A woman, 47 years of age, complained of weakness, glossitis and flatulence for four or five months. On admission the erythrocyte count was 28 million. The reticulocyte response to treatment could not be followed as the patient was ambulatory. The count reached the 45 million level after six weeks' treatment during which she received in all the material from 350 grams of liver (New York Hospital extract). During the following year the count averaged 40 million while receiving per month material derived from 300 to 600 grams (Lederle extract) alternating with New York Hospital extract derived from 200 grams. This patient has not experienced symptoms in spite of the relatively low count until within the past few weeks, when mild paresthesias were perceived similar to but less noticeable than those that had troubled her some years prior to treatment.

Comment The disease has been symptomatically controlled until within the past few weeks.

Case 21 A woman, 52 years of age, with an admission count of 3.7 million erythrocytes, was treated for 28 months after the red blood cell count had been stabilized, and during these months the average count was 4.2 million. The monthly intake consisted of the material derived from 300 to 600 grams of liver (Lederle extract) with intervals during which extract from 200 grams (New York Hospital extract) was used. This patient stated that the extreme weakness which she had experienced prior to treatment had entirely disappeared, and the paresthesias which had been severe had improved although they were still present and troublesome. Vibration sense on admission was reduced in both upper and lower extremities and was unchanged after a two year period of treatment. There was some loss of joint sense, and the heel to knee test was poorly performed. There was some impairment of cutaneous sensibility over the lateral halves of both legs and much mental depression and irritability. None of these features was altered during the maintenance period although the extreme mental confusion and lack of orientation present at the time of her admission to the hospital cleared following a few weeks of treatment.

Comment This must be considered an unsatisfactory result, both as regards subjective and some objective evidences of the disease. The blood reached 4.5 million erythrocytes at one time. Then the therapy was changed to ventriculin. The immediate response was good, but after return to liver extract the erythrocyte count dropped and remained below the desired level.

Case 36 A woman, aged 41, had been treated six months previously in the hospital, but because the count could not be maintained, she was readmitted with a count of 2.3 red blood cells. The maximum reticulocyte response of 17 per cent occurred on the eighth day, but the count never reached 4.5 million. Material from 3500 grams of liver was given during her month's stay in the hospital. During the 15 months following she has received amounts of material ranging from that derived from 200 grams (New York Hospital extract) to that from 400 grams (Lederle extract) within four week intervals. The erythrocyte level has averaged 3.9 million. With this relatively low level there have been no outspoken signs of the disease, and she has never shown evidence of central nervous system involvement. However, she has not felt in perfect health and has continued to tire easily.

Comment Although this patient was given somewhat more liver than the average patient, undoubtedly in view of her general symptoms of fatigue a larger amount should be given in an attempt to elevate the blood to a higher level. This patient was mentally depressed and undernourished. Whether these conditions had an indirect effect upon the production of erythrocytes is a matter for conjecture.

Case 24 A man, aged 36 years, was admitted with an initial count of 2.8 million red blood cells. The reticulocyte response was not obtained as the patient was ambulatory. The erythrocyte count rose slowly over a period of five months to a level of 4.5 million. This count was not maintained, however, and he continued to complain of flatulence and of vague gastrointestinal symptoms with much mental depression. The average count over a period of nine months was 4.3 million on a monthly total intake consisting of the material from 300 grams of liver (Lederle extract). The glossitis, which had been present prior to treatment, disappeared. The central nervous system remained objectively negative, and there were never any paresthesias. Following a change in his fortunes the gastrointestinal symptoms disappeared, and it

is possible that they were in part of functional origin, although the Graham-Cole roentgenogram of his gall-bladder showed the presence of adhesions

Comment Although this patient's blood count remained at a relatively low level, he obtained satisfactory symptomatic relief, and there was no apparent progress of his disease

Case 14 A man, aged 66, was under treatment for 15 months. His initial count was 1.4 million erythrocytes and the reticulocyte peak, occurring on the sixth day, was 30 per cent. There was a slow rise over a five month period during which he received material from 550 grams of liver (New York Hospital extract) in the first month, and in subsequent months that from 600 to 1200 grams (Lederle extract). Following the use of the Lederle extract from 1200 grams the erythrocyte count reached a level of 4.7 million, which, however, was not maintained with subsequent monthly doses of Lederle extract from 300 grams. The average count over a 12 month period was 4.3 million. In spite of this relatively low level he became symptom free at an early stage in his treatment, regained strength rapidly, and the diarrhea which had greatly troubled him disappeared. The paresthesias present intermittently for five years cleared entirely except on crossing one knee over the other when the pendent extremity became numb to a greater degree than he considered normal. No change, however, was observed in the hyperactive reflexes.

Comment This case is of interest because of the large amounts of liver necessary to raise the count temporarily to within normal limits, at which level it was not maintained with average amounts of liver. There was no evidence of progression of the disease and the patient was practically symptom free.

Case 10 A man, aged 60 years, stated that he had been troubled with weakness, exhaustion and paresthesias to a greater or lesser extent for three years. His erythrocyte count on admission was 1.9 million. The reticulocyte response rose to 38 per cent on the twelfth day, and in 11 weeks his erythrocyte count had risen to 4.5 million with the use of material from 600 grams of liver (Lederle extract). During the 32 months of treatment to date he received as an average monthly dose the material from 300 grams of liver (Lederle extract) alternating with New York Hospital extract from 200 grams of liver, and the level of his erythrocytes during this period was 4.6 million. The general symptoms were completely relieved, but the paresthesias persisted over the two year period of treatment and were described as a sensation of hot water on his finger tips and a band-like constriction around his knees. Vibration sense was reduced below the twelfth dorsal segment and absent over the knees, ankles and toes. Cutaneous sensibility was impaired below the twelfth dorsal segment. There was no improvement in the symptoms of central nervous system involvement during treatment, but, on the other hand, there was no progression of objective signs.

Comment An apparent arrest of moderately advanced subacute combined sclerosis with only fair hematologic response to treatment.

Case 12 A man, aged 84, gave a history of symptoms for nine months prior to his admission. During the first year of treatment his count averaged 4.1 million while being given the material derived from 500 to 600 grams of liver (Lederle extract) at monthly intervals. During the second year, the count averaged 3.6 million on extract from 600 grams of liver (Lederle extract) once a month. During the third and fourth years 4.4 and 4.6 million on extract from 600 to 800 grams of liver (Lederle) once a month. As supplementary treatment he was given six Lextron

capsules daily as well as whole liver in amounts approximating 230 grams daily. Although the amount of liver administered was large (at times he received extract from 300 grams twice weekly) the count was at no time above 5,000,000 red blood cells and the average for the total maintenance period falls below the normal as noted. His general response to this treatment was very satisfactory and his strength and sense of well-being were remarkable considering his advanced age. Incapacity from involvement of the central nervous system, however, progressed slowly; there was a gradual and progressive loss of vibration sense in the lower extremities, the paresthesias of the hands and the band sensation of the legs seemed at times more troublesome, the ataxia became more marked, the Romberg was persistently positive and the finer movements of the hands were performed with difficulty. The advance of these changes was so slow that it was scarcely perceptible to the patient who was able, in spite of his age, to carry on an active life as an actor in a federal project.

Comment It was impossible to control the progress of the disease in this aged man in spite of exceptionally large amounts of active principle.

Case 25 A man, aged 55, gave a history of symptoms referable to pernicious anemia for a year and a half prior to admission. The initial count was 3.2 million. The maximum reticulocyte count of 67 per cent occurred on the seventh day of treatment. There was a slow rise over a period of five months during which a total dosage consisting of the material derived from 3550 grams of liver was administered, 550 grams of which were extracted by the New York Hospital method and the remainder by Lederle. The average count of 4.6 million was maintained over a period of six months by the use of material from 600 grams of liver (Lederle extract) monthly, supplemented by a daily oral intake of 230 grams of whole liver and six Lextron capsules. During this time he became practically symptom free and stated with enthusiasm that he felt better than in many years. Paresthesias of a constrictive nature about the waist and thighs and numbness of his fingers disappeared within six months after his blood had reached the 4.5 million level, except as he repeatedly stated, when he smoked cigarettes, following which the paresthesias, especially in the legs, reappeared. Vibration sense was diminished in the lower extremities and did not return. The central nervous system was otherwise objectively negative.

Comment This case may be considered controlled although the erythrocytes have remained below the desired level.

Of these 10 patients whose erythrocyte counts did not measure up to the normal standard with therapy which is usually adequate, eight have apparently been fully controlled as far as symptoms and signs are concerned. In two the disease showed some evidence of activity. One of these latter showed slight amelioration of symptoms and the other evinced a slow progression of central nervous system changes. In this last case (case 12) it is possible that advanced age may have played a part in the resistance to treatment. As for the former (case 21) there was no objective evidence of advancing signs of the disease although the symptoms were only slightly improved by treatment. In commenting on case 21, it is only fair to point out that the same condition may exist in patients whose blood counts are at or above normal levels, as in case 29 which will be later presented in detail. This patient (case 29) had a normal red blood cell count and hemoglobin, although he had never received liver prior to admission. The symptoms likewise failed to respond to massive liver therapy although there was no ob-

jective evidence of progression. As regards the amount of liver given this refractory group of patients, it will be noted that none of these patients received less than the average amount of liver which served to maintain the blood of 70 per cent of the series at a normal level (Lederle extract from 300 grams of liver or New York Hospital extract from 200 grams of liver monthly), all of the women and three of the men received approximately twice the average amount and two patients received supplementary oral liver.

In contrast to the relatively large amount of active principle given these "refractory" patients, an occasional patient proved to be satisfactorily controlled from a hematologic as well as from a clinical standpoint on a much smaller amount of liver. The two cases which follow illustrate (a) the ease with which one patient was maintained on a small amount of liver (Lederle extract from 150 grams of liver) monthly and (b) in the second case, progressive improvement in the blood count on a constant amount of liver (Lederle extract from 300 grams, or New York Hospital extract from 100 grams) given over a period of three years. In the first case, since it was exceptional to obtain maintenance of a satisfactory count on such a small amount of material, the question arose as to whether the treatment might have coincided with a spontaneous remission. However, since the dose was not altered during a year's time and since Murphy obtained satisfactory results with equally small amounts of material it probably represents actual maintenance conditions.

Case 5 A woman, aged 55, gave a history of marked weakness, some dyspnea, sore tongue and periods of diarrhea. Paresthesias had not been present. On admission her erythrocyte count was 1.08 million. The maximum reticulocyte response of 33 per cent occurred on the eighth day, and the erythrocytes rose to 4.5 million in 13 weeks on a total intake consisting of the material from 2500 grams (New York Hospital extract from 1300 and Lederle extract from 1200). Thereafter her blood was maintained for one year to date at an average of 4.9 million red blood cells on material from 150 grams of liver (Lederle extract) at monthly intervals. Her symptoms cleared entirely and there were no objective signs of the disease.

Of interest also is the second case because the blood displayed an increasing rise of the erythrocyte level during the period of study (approximately three years) on a constant amount of liver, not exceeding the average monthly dose given the entire group (Lederle extract from 300 grams of liver). It would seem that a gradual storage of active principle may occur which yields a maximal hematopoietic effect only after some time has elapsed.

Case 4 A man, aged 59, sought medical attention because of extreme weakness and exhaustion. He had noticed transient paresthesias and stated that his sense of taste had become impaired—that all food "tastes and smells like rubber." His red blood cells on admission numbered 1.82 million, and the maximum reticulocyte response of 34 per cent occurred on the tenth day. The count rose to 5.1 million on material from 600 grams of liver (Lederle extract) in six weeks but thereafter dropped and remained at an average level of 4.5 million for six months on material from 300 grams of liver (Lederle extract) monthly. During the second six months the aver-

age count rose to 4.7 million, the following 10 months to 4.9 and during the 10 months to date it averaged 5.2 million. For a period of 20 months New York Hospital liver extract (derived from 100 grams of liver) was given at monthly intervals, during which time as well as during the time that the Lederle extract was given there was an approximate monthly increase of 30,000 erythrocytes.

The patient is entirely symptom free. His general strength is excellent and he states that his sense of smell has returned to normal. The paresthesias have practically disappeared. However, vibration sense remains impaired below the twelfth dorsal segment.

TIME REQUIRED FOR THE ERYTHROCYTE COUNT TO REACH 4,500,000 AND AMOUNTS OF LIVER USED

The group of 33 cases was analyzed to determine the length of time required and the amount of material used to bring the count to 4,500,000 red blood cells. Since some differences were observed that could not be entirely explained by the height of the initial count, an attempt was made to determine other factors, as for example the duration of the disease prior to treatment, which might be operating to delay the response to treatment. The estimated duration of the disease prior to treatment as dated from the first symptom noticed by the patient may be unreliable. In many instances the development of symptoms is so gradual that they may not be noticed until some unrelated event, such as an acute infectious disease, brings the symptoms to the patient's consciousness. Many patients, however, do offer a definite opinion as to when their symptoms began, and an attempt was made to correlate this with the time required to bring the count to normal. Some correlation will be noted. Of the 33 cases, 15 reached the 4.5 million level in two months or less. The average total amount of liver extract given was that derived from 670 grams (combined New York Hospital and Lederle extracts). The average initial count was 2.6 million erythrocytes. The duration of symptoms prior to treatment averaged 13.1 months. Of a second group requiring more than two but under three months to reach this level, there were 11 patients with an average initial count of 1.9 million. The average amount of material used in this group was that derived from 1072 grams (combined New York Hospital and Lederle extracts). The approximate duration of symptoms averaged 23.1 months.

A third group emerged from this analysis which was of considerable interest. This consisted of a number of patients who required more than three months for the erythrocyte count to reach the 4.5 million level. Many observers regard it as exceedingly unusual for the blood to fail to reach 5,000,000 within eight weeks, even with relatively small amounts of liver extract. Murphy found that 1 c.c. prepared from 100 grams of liver weekly was sufficient to raise the blood to the 5,000,000 level in eight weeks or less. In our group there were seven patients who required over three months to reach a count of 4,500,000 and to whom a minimum consisting of extract from 1600 grams and a maximum of extract from 6,600 grams of liver were

given. In these patients the average initial count was 2.9 million, and the slow rise is the more surprising in view of this high initial count. One patient in particular may be cited (case 36), who was given a total consisting of extract from 6,600 grams but whose count did not rise above 4.1 million in five months. In spite of this atypical response the diagnosis of pernicious anemia was retained as all other causes for her anemia had been excluded. Because of the special interest in this group of cases the details of these cases are summarized in the table. Other features in the clinical history or ex-

TABLE I
Cases Refractory to Treatment
(More than three months required for red blood cells to reach 4.5 million)

Case	Age	Duration of Symptoms (Months)	Initial Count	Time to reach 4.5m (Months)	Therapy (total grams)*	Remarks
12	84	9	3.6	9	5400	Senility
14	66	72	1.4	5	3860	Senility Frequent relapse in six years
24	36	12	2.8	5	2000	No CNS involvement
25	55	18	3.2	5	3000	Marked depression
27	68	72	3.9	4	1600	Chronic sinusitis Insufficient liver (?)
31	52	1—	3.7	4	900	Senility Malnutrition
36	41	1	2.3	5 to 4.1m	6600	Long history Insufficient liver (?) Marked depression (situational)

* Total of grams of liver, the extract from which (Lederle extract and New York Hospital extract) was administered

amination that were in any way unusual are enumerated in the column under the caption "remarks," although there is no experimental evidence that the rate of hematopoiesis is influenced by any of the factors mentioned.

It will be noted in the summary of the entire group that less than half of the patients showed a rise of erythrocytes to the 4.5 million level in less than two months. This result does not correspond with Murphy's experience, since all but two of his patients reached the 4.5 level in two months or less, and none failed to reach the 5 million level on amounts of extract between that derived from 500 to that from 1500 grams of liver (Lederle). The amount of liver extract used by our patients whose blood reached the 4.5 million level within two months was derived from 200 to 1500 grams of liver, but corresponding amounts failed to elevate the count of the remaining 18 of the 33 cases. Murphy states, "Failure of the blood to reach 5,000,000 or more within about eight weeks or less was usually due either to failure on the part of the patient to appear regularly for treatment or for blood counts at the proper intervals." Our patients reported for counts at weekly, bi-weekly or at the latest, monthly intervals so that it does not seem likely that

the erythrocyte rise to the expected point escaped detection, and in those with a slow rise, later counts served as a control for the earlier counts. All patients had been thoroughly investigated, the majority as pavilion patients in the hospital, before the diagnosis of pernicious anemia was accepted and active therapy instituted.

RESPONSE OF SYMPTOMS REFERABLE TO THE INVOLVEMENT OF THE NERVOUS SYSTEM

The most serious and persistent symptoms encountered in the routine care of the clinic patient with pernicious anemia are those that result from combined system disease or from peripheral neuritis. These may be the first to appear and often prove the most resistant to treatment. Neuropathologists are not in agreement as to whether a true peripheral neuritis exists as a basis for the paresthesias, although when these symptoms are mild and transient and tend to disappear with treatment it is customary to attribute them to a neuritis of the deficiency type. When, on the other hand, they persist in spite of intensive treatment and a normal blood picture, or slowly increase in severity, one cannot escape the conviction that they have their origin in a progressive involvement of the cord. Woltman,⁴ who has made an intensive study of the brain changes associated with pernicious anemia, in a personal communication has commented as follows on this point: "You have raised a question that has bothered me a great deal also, namely the source of the paresthesias. There is no question about the degeneration in the peripheral nerves described by Hamilton and Nixon⁵ but I am by no means certain that they always account for all the paresthesias these patients have. The progress of paresthesias associated with pernicious anemia in an upward direction until the lower portion of the trunk is included certainly suggests that they may also have their origin in the spinal cord as does the not infrequent failure to disappear more completely than they sometimes do on adequate treatment. The paresthesias often do disappear entirely, as might be expected in cases of degeneration of the peripheral nerves or where the spinal cord has not yet been too severely involved. That changes in the spinal cord may recede in some cases is proved by the occasional change of a positive Babinski sign to a negative one."

The subjective complaints from the paresthesias often seem out of proportion to the objective signs of cord involvement which may be so slight as to escape detection except by the most careful examination. For conclusive objective evidence not only of involvement, but especially as regards progression or regression, observations should be made at frequent intervals by the same examiner, as emphasized by Grinker and Kandel.⁶ Even under properly controlled conditions an evaluation of the findings is often extremely difficult. Vibration sense, two point discrimination, cutaneous sensibility are often unreliable in details, varying with the subjective interpretation of the patient not only from one examination to another but often

during the same examination. Objective signs offer more reliable criteria, and more significance may be attributed to such signs as a change from an ataxic to a normal gait, a decrease in sphincter disturbance, the disappearance of spasticity or a return to the normal of a Babinski reflex or of the Romberg sign.

Since the paresthesias often constitute the most troublesome symptoms and may persist after the general symptoms—the extreme exhaustion, the glossitis, the gastrointestinal manifestations,—have disappeared, they stand out in the patient's mind as an indication of whether or not the treatment is proving successful. Such symptoms consist not only of the familiar numbness and tingling but of various other abnormal sensations, among the most common of which is constriction, described as a band sensation around the body or the thighs or legs, occasionally around the head. Such expressions as "my head feels tight as a drum," "my chest seems in a vice," "legs feel as if they were bound and would burst" are common. An abnormal temperature sensation "as if my hands were in hot water" or "my feet feel as if I were walking on ice although they are not really cold" often is described. Extreme hyperesthesia occurs—"if the cat brushes against my legs it causes acute pain." Difficulty in walking may result from spasticity or from an altered position sense—"I am not sure where my feet are when I take a step." Defective sense of position gives rise also to such expressions as "I lose my legs in bed," "cannot sew because I do not feel the needle or know where it is going." Altered cutaneous sensibility in the feet is not uncommon, so that the patient feels that he is "walking on cotton," or "standing on a rubber ball," or the "hands feel as if they were stuffed." Occasionally actual pain is experienced, often in the legs or back. One patient described acute pain shooting from the soles of the feet up into the calves of the legs. Because of the severity of these symptoms various measures have been employed, but for the most part with little success. They have ranged from the use of large amounts of vitamins to various physical therapeutic measures. In one patient who complained of severe pain in the back roentgen-ray therapy was utilized with the hope that this method of treatment which is occasionally effective in certain types of intractable nerve pain might prove helpful in relieving the symptoms. No appreciable improvement was experienced. In those patients showing mild cerebral manifestations, such as depression, apprehension and irritability, a sedative often was beneficial. As a rule, marked cerebral disturbances, such as confusion, memory defects, paranoid tendencies or delusions, disappeared during the initial treatment.

Of the total series of 36 patients in this group, eight never experienced subjective symptoms other than transient paresthesias. Four were entirely relieved of such symptoms which varied in degree, 15 were considerably improved although not entirely free, in five the symptoms were unchanged and in three they became definitely worse. In one, although the paresthesias

were relieved, shooting pains had developed in the legs. As regards objective signs of the disease, as far as they could be determined by the clinic records, only one showed definite progression of the disease (a man aged 84 years), 17 were unchanged, in eight there was apparent improvement, and in 10 objective signs of involvement of the central nervous system had never been detected.

Not infrequently one encounters the report of subacute combined sclerosis not associated with the blood picture of pernicious anemia but apparently due to the same cause. If the etiologic factor is identical with that which produces the anemia, it is interesting to note that the severity of the central nervous system disease does not necessarily parallel the severity of the anemia. Nevertheless it is assumed that amounts of active principle which will elevate the blood to 5,000,000 or above will prevent the progression of central nervous system changes. When, however, the blood count has never been reduced, the count obviously cannot serve as an index of adequate treatment, and sufficient active principle is given, or more than necessary, to maintain the count at a high normal level, because of the empirical observation that if the blood is so maintained the central nervous system disease is held in control. Castle and Minot⁷ summarize our lack of knowledge of this phase of the disease as follows, "Until the hematopoietic principle of liver is isolated it will be impossible to find by therapeutic test whether it is also specific for the neural disturbance, or whether multiple factors, either intrinsic or extrinsic, are involved." The following case affords some evidence that progression of combined sclerosis may be held in abeyance by the administration of active principle. This patient has been under observation and treatment for three years. Although he has not been relieved of his symptoms—indeed he states that the paresthesias have become more severe—there has been no objective evidence of progression and the return to normal of the ankle jerks and of the Babinski reflex would indicate that some actual improvement had occurred.

Case 29 A man, aged 63, for a year and a half prior to admission had noticed great weakness, diminished power in his lower extremities and marked paresthesias of his hands and feet as well as a sense of constriction in his thighs. He dated the onset of his symptoms from an acute respiratory infection. Examination revealed markedly increased tendon reflexes with a positive Babinski. Position sense was very faulty and the Romberg sign was positive. Ataxia was marked, and he was unable to walk because of this and as a result of weakness. Vibration sense was greatly diminished in his lower extremities. He had never received liver or any other treatment. His hemoglobin estimation was 11.6 grams, red blood cells numbered 4,800,000, reticulocytes 12 per cent. The hematocrit reading was 46 vol per cent, and the volume index 1.1. There were some macrocytosis and anisocytosis. No free hydrochloric acid was demonstrated in his gastric contents with histamine stimulation. The spinal fluid did not impress the neurologist who saw him as of diagnostic significance, although the protein content was slightly increased and the colloidal gold curve appeared as 2222111111. There were 245 c.c. of residual urine, and the renal functional tests yielded normal values. The diagnosis was that of subacute combined sclerosis, and liver extract was given by intramuscular injection.

His general condition rapidly improved so that when he left the hospital he was able to walk without assistance. He has continued to feel very well generally but his paresthesias have persisted as well as the spastic gait and some degree of ataxia. He has received material from 600 grams of liver (Lederle extract) at monthly intervals as well as six Lextron capsules and whole liver daily (approximately 230 grams). Large amounts of vitamin B have been included in his diet. His erythrocytes over a period of 19 months have been maintained at an average count of 5,000,000. The sense of tightness, coldness and numbness of his hands has persisted, but a recent neurological examination, although unchanged in other respects, reveals that his Babinski reflex has returned to the plantar response and that the ankle jerk is of normal amplitude.

DISCUSSION

This study of the response of 32 patients with pernicious anemia to definite amounts of potent factor brings out several points of interest. It was thought on the basis of the satisfactory response of the majority of patients, as well as on the basis of the experience of other workers, that the average amount of material used (Lederle extract of 300 grams of liver or New York Hospital extract of 200 grams of liver per month) was ample, and indeed, in excess of what was required for adequate maintenance of the blood at normal erythrocyte levels. It was a surprise, therefore, to find that approximately one-third of the patients of this small series showed average red blood cell counts below the standard of normal. The majority of these "refractory" cases (eight of the ten) were given approximately twice the amount of material received by the other 22 patients who showed a "normal" response (an average of Lederle extract from 600 grams as against that from 300 grams of liver per month) as well as in several instances, supplementary liver by mouth in an amount, in itself, often found sufficient to maintain the average patient. It must therefore be concluded, since this unequal response occurs in a fairly large number of patients, that each patient with pernicious anemia must be managed as a separate problem and the dose individualized on the basis of the trend of the erythrocyte count averaged over stated intervals of time. The fact that the disease in eight of these ten "refractory" patients with low average erythrocyte values was controlled from the standpoint of signs and symptoms would make it appear that for some individuals a slightly substandard level of the erythrocyte count under treatment is not inconsistent with a satisfactory state of health. Nevertheless, the low level of the erythrocytes should be recognized and every effort made to elevate and stabilize the blood at a higher level. The possibility of relapse in these patients with severe damage to the nervous system, even when apparently under control, should never be forgotten. In our series, fortunately, no such serious relapse has occurred.

A second point of interest developing from the study consisted in the time required to bring the initial count to the minimum normal level. Although the majority of the group reached this minimum level within three months, and 15 within two months, in general the time required was in

excess of that reported by Murphy, who used corresponding amounts of material. In seven patients of our series even longer periods of time than three months elapsed before the red blood cells reached 4.5 million. Although, again, the amount of material was the same or more than that given the majority of the group and the initial count in several instances was not low, the blood of these individuals rose more slowly than it did in other instances where the initial count was considerably lower. These patients had been carefully studied and the diagnosis satisfactorily established, in several the pernicious anemia had been recognized and treated some years previously, but they were in relapse when the treatment which forms the basis for this study was begun. No satisfactory explanation can be offered for the atypical response of these patients, but many of them were additionally handicapped by some outstanding condition other than the pernicious anemia, as for example, a continuous depressive state arising from an unfortunate domestic or financial situation or by malnutrition or senility. Whether such conditions do actually influence the rate of hematopoiesis is a matter for conjecture. Whatever the cause for these retarded responses, it would seem that no unqualified prediction can be made as to the length of time necessary to bring the count to normal on the basis of the level of the initial count or as estimated by the response of the average patient.

It would seem also that the effect of treatment upon the neurological aspects of the disease cannot be predicted. Senility, in one case in this series, in the presence of a fairly well elevated and sustained erythrocyte level, seemed responsible for the unsatisfactory result in controlling the central nervous system disease. The extent of central nervous system involvement may not parallel the red blood cell count. Several patients who had had repeated hematologic relapses did not show evidence of neural disturbance, whereas the most advanced case of combined sclerosis in the series had never been anemic. The difficulty of following the course of the combined system disease makes it imperative that careful, detailed and frequent neurological examinations be made and that maximal amounts of potent material be given these patients regardless of the height of the red blood cell count.

Finally, this study demonstrates that although the more concentrated material is more satisfactory for use because of its greater freedom from unpleasant reactions, it is not equal in potency to the unrefined preparation. Whereas material from 100 or 200 grams of liver represented in the unrefined preparation controlled the average case, an amount of concentrated preparation derived from 300 grams of liver was required for equally good results. Potent factor undoubtedly is lost in refining and in concentrating the material, and the amount available in the various preparations cannot, therefore, be measured accurately by the weight in grams from which the material was derived. In view of this variation in potency which depends upon technical methods of extraction and refinement, it is advisable to record not only the weight in grams represented by the preparation, but the specific brand employed.

CONCLUSIONS

1 The average red blood cell count of 32 patients with pernicious anemia was 4.5 million for women and 4.83 million for men after hematopoiesis had been stabilized by treatment. The average amount of material used was Lederle extract derived from 300 grams of liver or New York Hospital extract from 200 grams per month.

2 Ten of the 32 patients showed erythrocyte values below normal standards although active principle much in excess of what was adequate to control the average case was given. However, in eight of these ten cases the disease appeared to be clinically controlled.

3 The length of time required to bring the blood count to 4,500,000 was two months or less in 15 patients and between two and three months in 11. The initial count of those requiring two months or less was 2.6 million, of those requiring between two and three months the initial count was 1.9 million. Seven patients required more than three months to bring their count to normal. The poor general condition of these patients, due to various causes other than pernicious anemia, may have had a depressing effect upon the rate of hematopoiesis.

4 Of the total series of 36 patients only eight had never experienced symptoms of peripheral or central nervous system involvement. Following treatment, of 28 who experienced symptoms, four were entirely relieved, 15 were improved, in five there was no change and in three they became worse. In one the result was indeterminate. It will be seen, therefore, that although the majority of patients are benefited by treatment, no absolute prediction as to relief of symptoms can be made.

5 In spite of intensive treatment one patient showed progression of objective signs of central nervous system involvement. In 17 the signs were unchanged, in eight there was apparent improvement. In 10 patients there were no objective signs of neural disturbance.

6 Although patients may be free of signs and symptoms of pernicious anemia with average counts slightly below the normal, the fact that two patients with such levels showed evidence of beginning relapse indicates that a continued effort should be made to elevate and maintain the blood at a high level.

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ARACHNODACTYLY AND STATUS DYSRAPHICUS, A REVIEW *

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PART I ARACHNODACTYLY

THE clinical picture of arachnodactyly as described by Marfan is so characteristic that one having it in mind could hardly fail to recognize it. Since the original description little has been added, there have, however, been an increasing number of case reports in recent years. We have been able to find but 13 reports of the disease in the English-speaking literature since 1903 and of these only three came from this country. It becomes apparent then that the condition is relatively unknown on this continent and it is equally true that the diagnosis will be made more often as our familiarity with it increases. Lloyd¹ gave in his recent article such an excellent résumé of the subject that this paper would hardly be justified were it not for the fact that an entirely new significance has attached itself to the condition through a new idea of Passow. This will be reviewed in the second half of this paper.

The essential feature of arachnodactyly is the striking length and slenderness of the extremities, especially of the hands and feet. To this is added the invariable accompaniment of other congenital defects such as cardiac or pulmonary anomalies, webbed fingers, highly arched palate, muscular dystrophy, spurring of the os calcis, and ectopia lentis. The condition apparently has its onset during intra-uterine life since in the majority of cases the typical thinness of the extremities is noted at birth. There does not seem to be a predilection for any particular sex. Weve² in 1931 found that of 82 cases reported to that time, 40 were females and 42 males. Most of the patients (about 50 per cent) are below the age of ten. However, Weve found 20 cases between 10 and 20 years of age. Two of Weve's cases were 40 and 62 years old, respectively, and Omond's case was forty-seven.

The first description of the syndrome came in 1896 by Marfan³ who gave it the name "delichostenomelia". He also used the exceedingly apt term "Spider Feet" because of the likeness of the narrow fingers and toes to spider legs. In 1902 Mercy and Babonneix⁴ suggested the name "hyperchondrioplasia". Achard⁵ called the condition "arachnodactyly" and this term has been accorded more frequent use than the others. Weve felt that all these terms expressed only part of the clinical picture or were prejudiced concerning the underlying pathology. He believed "congenital mesodermal dystrophy" a better term but preferred simply to use "Marfan's syndrome".

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CASE REPORTS

Case 1 R M, a boy, aged six, had poor vision all his life. It was impossible to ascertain the vision in the usual way, due to his poor mentality, but it was evident from the way he used his eyes that he had very little sight. He was a tall slender child. The extremities were slender and the fingers and toes unusually long. There was webbing of the fingers. The muscles were poorly developed and this added to his appearance of thinness. The skull was dolichocephalic with prominent forehead and flattened occiput. The palate was highly arched. There was moderate kyphosis and moderate left scoliosis of the thoracic spine. The scapulae were winged. The thorax was of the asthenic type, flat and narrow. There was no deformity of the thorax, no acrocyanosis, no deformity of the feet or spurring of the os calcis. The nipples were symmetrical.

There was a dislocation of the lens in each eye downward and to the left. The pupil was small but reacted promptly to light and dilated well with mydriatics. The lenses were hazy and dotted with punctate opacities. The iris, O U, was tremulous. Cooperation was very poor but we were able to determine retinoscopically that the eyes were approximately 20 diopters hyperopic. At later examinations we noted that the lenses seemed to change position rather easily. There was no indication of heterochromia or Horner's syndrome. The boy was obviously defective mentally and a psychological examination was made by Dr. M. B. Weiner who concluded that there was cerebral maldevelopment. A considerable improvement in the boy's mental reactions was noted after he had worn 15.00 D spheres before each eye for several weeks.

Case 2 G K, a boy, aged five years, had always held things close to his eyes in order to see them. This patient was seen only once and our examination was incomplete. We are indebted to Dr. D. M. Stiefel for additional data. His complaint was that he tired easily when standing or walking, and that he had poor vision. He complained also of his legs and feet hurting. The most striking feature was the general hypotonicity of his skeletal musculature. This was exemplified by his great weakness and by the hyperextensibility of his wrists, ankles, elbows and hips. His hands and feet were unusually long and slender, and the fingers and toes were thin and tapering. The external ears showed a deficiency of the cartilage and deformity of the helix. The palate was highly arched. The skull was dolichocephalic. The scapulae were winged and the spine showed moderate scoliosis. There was a definite lack of subcutaneous fat which added to his wasted appearance. According to Dr. Stiefel the boy had a congenital heart defect.

Examination of the eyes showed bilateral iridodonesis. The pupils were small and responded poorly to homatropine. The lens on each side was luxated temporally. The fundus details could not be seen, and retinoscopy was difficult. Vision was 20/200 in each eye and was not improved with lenses, although the retinoscopy suggested a high hyperopia. The patient was not seen again and no further examination was made.

Case 3 Mrs. F B, a woman aged 37 years, had high myopia and dislocation of the lens in each eye, and detachment of the retina in the left eye. The patient was an exceptionally thin tall woman and her arms and legs were unusually long and slender, a fact which had been noticed shortly after her birth. The slenderness of the limbs was most marked distally and the fingers were typically "spider fingers" of the type seen in arachnodactyly. The phalanges were most involved. The skull was long and narrow. The hard palate was highly arched. The thorax was narrow, flat, and tapered toward the waist. There were no deformities. The scapulae were winged markedly. There was slight scoliosis of the dorsal and lumbar spine. The breasts were symmetrical and equal in size. Auscultation revealed a loud blowing systolic murmur at the cardiac apex. Her feet were unusually long and she stated when she bought shoes the salesman always mentioned the fact. There was no spurring of the

os calcis There was a noticeable lack of subcutaneous fat over the body The hands and feet were moist and warm All the joints showed hyperflexibility Roentgenograms of the hands and feet showed normal bone structure but the phalanges and metacarpals and metatarsals were slender and tapering The patient's father was not seen but he was said to be very tall and thin with long hands and feet He was said to have become blind "from glaucoma"

Vision O U equalled perception of light Projection of light was excellent with the right eye but very poor especially in the lower field, with the left eye In the right eye the anterior chamber was deep and the iris tremulous The pupil reacted well to light but did not respond well to a mydriatic The lens was densely white and opaque, and trembled with movement of the eye The direction of its dislocation was not ascertained since the pupil did not dilate well and a slit lamp examination could not be made In the left eye the anterior chamber was deep and there was iridodonesis The pupillary reaction was normal but its response to mydriatics was sluggish The pupil was aphakic The lens could be seen with the ophthalmoscope, lying in the vitreous below The retina above was detached, the detachment involving the upper half of the fundus and extending downward covering the macula There was no heterochromia or Horner's syndrome in either eye

Case 4 E T, a boy of 20, had poor vision all his life, with $+8.00 +3.00 \times 120$ V O D = $6/30$, $+6.00 +3.00 \times 90$ V O S = $6/30$ but could not be improved He showed bilateral dislocation of the lens, iridodonesis, and sluggish response of the pupils to mydriatics The lens O D became dislocated into the anterior chamber and was removed but vision could still not be improved

The fingers were long, thin and tapering and the arms were long The span of his extended arms was four inches greater than his body length The palate was highly arched He showed no deformity of the thorax and there was no evidence of any heart lesion The feet were long with long toes No spurring of the os calcis The muscles were well developed

Shortly after the lens O D was removed he suffered a skull fracture in an automobile accident At this time he developed detachment of the retina O D Since that time he has been operated on several times elsewhere for meningeal adhesions, to relieve epileptic attacks

Case 5 L T, a girl nine years old, sister of case 4, showed a bilateral dislocation of the lens downward The pupils did not dilate widely after instillation of homatropine There was iridodonesis O U The fundi were negative Vision O D = CF at 6 ft and O S = CF at 3 ft A $+10.00$ D^s each eye brought the vision up to 20/200 but it could not be further improved The hands were rather gracile with tapering fingers The feet were not unusually large The palate was rather highly arched The scapulae were winged and she showed an indentation near the lower part of the sternum suggestive of funnel chest There was slight scoliosis No evidence of heart disease, no deformities of the ears, no spurring of the calcaneus The muscular system was not abnormal

The mother of these two patients also had subluxation of the lens but showed no other evidence of the disease

Relatively few cases of arachnodactyly were reported in the early years following the first description Rietschel⁶ in 1917 found nine cases in the literature and in 1928 Carrau⁷ found but twenty Weve added 23 of his own cases in 1931 to the 60 previously reported Twenty-two additional cases have appeared since 1931 Arachnodactyly is definitely familial In the early cases this was not noted but more recently it has been found that practically all patients have other members of the family exhibiting char-

acteristics of the disease Lloyd¹ reported five cases in a family of six, King⁸ described three cases in one family, and Viallefont and Temple⁹ presented four members of one family with the condition Weve's 23 cases belonged to six different families, in each of which more than one member was involved

The etiology is not known Some authors believe it is an endocrine disorder, placing greatest importance on the pituitary gland Many of the essentials of the condition such as the long jaw, the long limbs, the hypertrophied ears, lend support to this idea, but the thinness of the bones is in direct opposition to it One author expressed the opinion that dysfunction of the pituitary caused acromegaly in adults, gigantism in infants, and arachnodactyly in fetuses Young discredits the pituitary theory since with few exceptions the onset takes place in intra-uterine life It has been stated that disorders of the endocrines cannot affect the fetus because of compensation by the mother It might be assumed that since the condition is definitely familial, derangements of the maternal glands might be a factor, but in most cases not all the offspring in a family are involved In cases where roentgenograms have been taken of the skull, the sella has not been found unusual The co-existence of so many varied signs is against the possibility of a pituitary fault¹⁰

The only other endocrine gland upon which the blame might be placed is the parathyroid It might be thought possible that the skeletal anomalies of the condition are due to a disturbance of calcium metabolism However, no evidence of such a pathogenesis was found in any of the cases in the literature

Several authors have likened arachnodactyly to mongolism, apparently because a few cases were reported with narrow palpebral fissures This idea is not acceptable, especially in view of the truth that the great majority of cases are of normal mentality

The condition is similar in some respects to congenital muscular dystrophy and it is true that the two must be closely allied In true congenital muscular dystrophy, however, there are rarely other congenital anomalies Young reported that in arachnodactyly the muscular electrical response was fairly normal, as opposed to the poor response in muscular dystrophy The typical case of primary muscular dystrophy begins in youth and is progressive, progress of the dystrophy in arachnodactyly has never been reported

The most popular conception of the pathogenesis is that there is a selective dystrophy of the mesodermal tissue On this basis Weve explained the involvement of the bones, tendons, ligaments, muscles, connective tissues, fat, heart, and blood vessels Other authors have recognized this explanation but felt that the idea of mesodermal dystrophy did not satisfactorily explain the involvement of other tissues which are not mesodermal in origin Kallius¹¹ felt that mesoderm, ectoderm, and entoderm were all involved As we will point out later, it is possible to explain all the findings on the basis of mesodermal maldevelopment

Piper and Irvine-Jones¹² expressed a more general conception of the etiology. They felt that a disease entity with so many and varied manifestations must be due to pathologic defects of the germ plasm originating in embryonic life when dependence on the maternal organism is complete. The hereditary nature of the disease is clinically undisputed and Weve feels that whatever the direct cause may be there is a hereditary factor.

As to the symptoms we find the extremities long and slender. The involvement increases distally and the phalanges and metatarsals and metacarpals are unusually long and thin and tapering.

Roentgenograms show the unusual thinness and slenderness of the long bones of the hands and feet, but otherwise are usually negative. In most reports the bony structure has been recorded as normal, although a few observers have noted an increased rarefaction and decalcification. The length of the long bones of the arms and legs is not only increased as compared to that in normal persons but there is also a relative increase in proportion to the length of the trunk. Webbing of the fingers is often present and acrocyanosis of the extremities has been reported frequently. The muscular development of the whole body seems to be deficient, the general muscular weakness sometimes being so great that it has been compared with that of amyotonia congenita and congenital muscular dystrophy. Most authors find kyphoscoliosis which increases as the patients grow and is due to the great muscular weakness rather than to any changes in the bony spine. Laxity of the joint ligaments is frequent, most patients exhibit hyper-extensibility of the joints, and dislocations are not unusual. Flexion contractures are due to contractions of the tendons and occur most often in the fingers. The thorax is usually of the asthenic type, flat, narrow and funnel-shaped, with delicate ribs. The scapulae are winged. The skull in most cases is dolichocephalic, although Piper and Irvine-Jones reported a case in which the skull was brachycephalic. The ears may show abnormalities in size or shape of the lobes. Usually the bony palate is highly arched. The calcaneus is occasionally spurred.

The occurrence of congenital anomalies of the heart and lungs seems not to be unusual. Two cases have come to necropsy. Boeiger's case¹³ showed a patent foramen ovale, and only two lobes in the right lung. In Piper and Irvine-Jones' case congenital lesions of the heart and failure of normal divisions of the lungs into lobes was found. Besides these cases, others^{10,13,14,15,16} showed clinical evidence of heart disease. Also in this regard it is interesting to note that several reported cases have died of pneumonia.

The ocular signs in arachnodactyly are most interesting and form a definite part of the clinical picture. The most frequent finding is the congenital dislocation of the crystalline lens. Weve found this defect in 25 cases in 1931. In our review of 105 cases in the literature it has appeared 45 times although possibly some of the cases are repetitions. Weve felt after thorough study that Pfaundler's case¹⁴ was identical with Boeiger's first

case,¹⁷ and that Cameron's case¹⁷ had previously been reported by Ormond and Williams¹⁸. It is also possible that Fleischer's¹⁹ and Thaden's²⁰ cases were identical. In our review we ignored these possibilities and considered all reported cases as distinct. The dislocation is usually bilateral and is always congenital though it may not be noticed for years after birth. The lens may be found luxated in any direction. Two cases (Thaden and Weve) have been noted where the luxation was completely into the vitreous and one of our own cases was found in this serious state. Others have reported a dislocation into the anterior chamber and this complication occurred in one of our own cases also. The incidence of ectopia lentis in arachnodactyly is probably considerably higher than 50 per cent. In the earlier cases the defect was not looked for and in other cases the eyes were not mentioned. In only 14 cases were the eyes reported as being normal and in some of these the recorder mentioned that the pupil did not respond well to mydriatics and a good intra-ocular examination was therefore impossible. A few authors^{2, 19, 20, 21} have noted that the lens is almost always reduced in size. King noticed a coloboma of the lens in two cases and Weve also mentioned the occurrence of this defect.

The pupil is often small and sometimes ectopic. The iris shows a sluggish response to the instillation of mydriatics. Doubtless this is due to maldevelopment of the dilator pupillae muscle. Iridodonesis is present in cases showing ectopia of the lens. Paralysis of accommodation has been reported by Weve and pupillary membrane remnants are found fairly frequently.

Other ocular signs in arachnodactyly are not consistently present. Although in some cases the refractive findings were not recorded it seems that most of the patients were myopic, sometimes the myopia being as high as 60 diopters (Weve). Boerger's first case showed a myopia of 16 and 20 diopters in the right and left eye respectively. Cameron, Ormond and Williams, Thaden, and de Hass²² reported cases with high myopia. In contrast to this, Bier's case²³ (in which there was no luxation of the lenses) showed a hyperopia of 9 diopters in each eye and Padovani's case²⁴ and several of Weve's were hyperopic. The refractive error cannot be given too great consideration in any case, however, since it may often be influenced by the abnormal position of the lens. Piper and Irvine-Jones recorded the occurrence of short lower lids in their patients. Nystagmus has been frequently mentioned and is probably due to the poor vision which most of these patients have. Other ocular signs such as nystagmus, fundus lesions, and megalophthalmos which have been mentioned, probably do not occur with greater frequency than in other groups of patients. Usually the orbits are large and there is a small amount of orbit fat, producing a sunken appearance of the eyes, which together with the long, thin face gives the patient an aged look and an appearance of suffering.

If any ocular manifestations throw light upon the etiology it must be

the ectopia lentis, since this occurs more often than other ocular defects. As noted above, the most generally accepted theory of the arachnodactyly is that the disease is due to a selective mesodermal dystrophy. The theory has been rejected by some investigators, however, since there are tissues involved (lens, zonular fibers, and iris) which are not mesodermal in origin. It can, however, be shown that the ocular defects in arachnodactyly may be explained on the basis of a mesodermal maldevelopment. There are two ways in which this may be done.

It is supposed by Treacher Collins²⁰ that the fibers of the suspensory ligament of the lens are originally cellular adhesions between the lens and ciliary processes, and that as the eye grows these stretch and develop into fibers. Dislocation of the lens could then be due to defective development of the suspensory ligaments in the third or fourth month of fetal life. If the adhesions are weak or absent in one part of the circumference of the lens, then the fibers opposite, instead of stretching will pull the lens in that direction. If the suspensory fibers are absent they will not be seen in the pupillary space attaching to the free border of the lens. According to Ida Mann²⁶ "the main factor in the production of absence or weakness of the suspensory ligaments appears to be a persistence for an abnormally long time of one, several or all of the vessels which usually connect the *circulus arteriosus iridis major* with terminal branches of the hyaloid artery around the edge of the optic cup. These vessels appear at the fifth week and begin to disappear at the middle of the third month of embryonic life. It appears then that such a defect as coloboma, or weakness of, the zonular fibers is due to causes arising in the second or third month—are remote from endocrine causation—and are developmental anomalies." It is seen from this that congenital dislocation of the lens can be explained by an anomaly of the embryonic vascular system, a mesodermal derivative. There are cases of arachnodactyly reported which showed ectopia lentis, in which the zonular fibers could be seen in the pupillary space attaching to the border of the lens. In these cases the ectopia lentis was obviously not due to absence of the zonular fibers but it could have been due to weakness of them. Moehlig is in agreement with this idea. He says, "the lens, while it is ectodermal in origin, could readily be affected by the mesodermal supportive tissues being weakened"³²

Perhaps a better way to explain the ocular defects was mentioned by Weve. He expressed the opinion that the dislocation of the lens is not due to a defect of the zonular fibers but rather to the small size and spherical shape of the lens. Since in many reported cases the zonular fibers were normal, this idea is acceptable. Passow pointed out that this microphakia could be a manifestation of a general mesodermal dystrophy. We know that the embryonic lens is surrounded by a rich vascular membrane, the *tunica vascularis lentis*, the anterior part of which is the pupillary membrane. The arteries of this tunic, as well as those of the iris, originate from the

long posterior ciliary arteries and anastomose with branches of the hyaloid artery. Hence it is conceivable that any dystrophy of the mesoderm in embryonic life could cause dystrophic changes in the *tunica vascularis lentis* (a mesodermal derivative) and so to the lens and the iris.

We have suggested here a theory of the causation of arachnodactyly which explains all the usual findings in the disease. The theory is not new; we have only endeavored to adapt it to the whole picture. A brief summary of the salient features of the literature on the subject and reports of five cases are also presented.

PART II STATUS DYSRAPHICUS AND ITS RELATION TO ARACHNODACTYLY

New significance has recently been attached to arachnodactyly by Passow²⁷. He considers arachnodactyly as identical or closely related to status dysraphicus, or "microform of syringomyelia," basing his belief on the similarity of the signs and symptoms of the two conditions. The entity of status dysraphicus being practically unknown in the American literature it seems necessary to give here a brief outline of the condition before discussing Passow's idea of its similarity to arachnodactyly.

The first suggestion that faulty closure of the neural tube (spinal dysraphy) might be an etiological factor in many of the hereditary neurological diseases was made by Henneberg, who demonstrated that in syringomyelia the spongioblastomas are united at the spinal raphe. He felt also that syringomyelia was a dystrophy of the spinal cord.

Syringomyelia consists in the proliferation of glial cells in the central region about the central canal of the spinal cord and medulla. This central gliosis characteristically breaks down into a cystic cavity. It is believed (Henneberg) that the gliosis arises from embryonic cell rests in the spinal cord, such cell rests being present because of faulty closure of the neural tube. Hence the term "dysraphy."

Following the recognition that syringomyelia is a dysraphy of the spinal cord Bremer²⁸ searched in patients with syringomyelia and in their families for developmental anomalies which would seem to result from a spinal dysraphy. He found a considerable number. There was a preponderance of the span of the extended arms over the body length. One of the most characteristic signs was the funnel chest and almost invariably associated with this defect he found acrocyanosis. The hands were usually moist and cold. Further there was frequently a kyphoscoliosis which might be due either to trophic or muscular disturbances. Winged scapulae and webbed fingers were of more than occasional occurrence. Another frequent and quite typical sign was a difference in the mammae, one mamma being smaller than the other and the mammilla showing less pigmentation. Finally there was spina bifida often associated with enuresis nocturna, anomalies of the ears, highly arched palate, and other signs usually referred to as stigmata of degeneration.

Bremer found these signs not only in cases of typical syringomyelia, but also in quite a number of "normal" people, and, whenever he found one of these symptoms there was always an accumulation of others belonging to the same group. None of these cases could be diagnosed as true syringomyelia though most of them showed some disturbances of pain and temperature sensation, and quite frequently some anomalies in the muscular system. But the characteristic symptom of syringomyelia, the progression, was absent in all of them. On examining other members of the family, typical syringomyelia was found in several instances, and almost every member of the family showed some of the symptoms described above. All these facts led Bremer to assume that there is a well defined syndrome that is definitely hereditary in character and that forms a continuous line from the normal individual to the definitely pronounced case of syringomyelia.

Since most of the structures involved, the sternum, the breasts, the spine and spinal muscles, the palate, and the spinal cord are midline structures he calls this syndrome "status dysraphicus" believing them to be due to faulty formation of the spinal raphe.

It was of course difficult to draw any conclusions as to the pathological changes that took place in the spinal cord of these patients, since they were of no serious nature and did not come frequently to autopsy. Therefore Bremer²⁹ followed all the cases which came to autopsy in the Pathological Institute in the University of Munich for some time and picked out those which showed any suggestive sign of status dysraphicus. He examined four cases, three of which showed increased glial tissue in an area which lay behind the central canal but did not reach the posterior horns. The difference between these and normal sections of the cord was not absolutely significant, only a few glial cells and mostly fibers being seen. The fourth case showed hydromyelia of the spinal cord. The changes were mostly in the cervical portion, few alterations being observable in the lumbar region. The most significant feature was a proliferation of the ependyma in the central canal. Examining relatives of these cases, in each particular family a few members could be found who revealed the typical picture of status dysraphicus.

The clinical picture of status dysraphicus was first brought to the attention of the ophthalmologist when Passow²⁷ published his classical studies in 1933. In addition to mentioning the general symptoms of status dysraphicus described by Bremer, he noted also the frequent occurrence of Horner's syndrome and heterochromia iridis. In 50 patients with Horner's syndrome and heterochromia he found signs of status dysraphicus in 80 per cent. Later he added more cases and in the whole series found signs of status dysraphicus in an even higher percentage. Anomalies of the sternum, especially funnel thorax, were common. Kyphoscoliosis, winged scapulae, and webbed fingers occurred frequently, often together. In most patients the span of the extended arms was greater than the body length. Differences in the size and position of the breasts were noted.

In fairness to the facts it should be mentioned that Horner's syndrome and heterochromia, while being found not infrequently in status dysraphicus do not occur as often as it may seem from reading this review. In most textbooks Horner's syndrome and heterochromia are given hardly more than passing mention as symptoms in syringomyelia. Bremer in his studies found them in only a low percentage of cases of status dysraphicus. In this review we have stressed their occurrence since they are of great interest to the ophthalmologist. Passow's work gives the impression that these symptoms occur with greater frequency than is really the case. In searching for cases of status dysraphicus Passow used these symptoms as a guide and accordingly they occurred in a high percentage of his cases. It does not follow that they occur in all or most cases of status dysraphicus.

Passow felt that these cases offered clinical proof that the Horner's syndrome and the heterochromia could be explained by the same etiology as the other symptoms of status dysraphicus. He attempted also to supply experimental proof. Up to that time the question of whether heterochromia iridis might be the result of sympathetic paralysis had not been definitely settled. Many authors were unable to produce a depigmentation of the iris by sympathectomizing animals. Other investigators on the other hand had shown that interruption of the cervical sympathetic resulted in heterochromia. Passow, in his thorough experiments, showed that heterochromia followed a paralysis of the cervical sympathetic only when the paralysis occurred before development of the anterior layer of the iris and its pigment. He excised a portion of the right cervical sympathetic in young animals. Two or three months after the sympathectomy a lack of color was perceptible in the homo-lateral iris in those animals which were between six and eight days old at the time of the operation. In older animals, however, no heterochromia developed. Microscopical study of those irides which showed heterochromia revealed a decrease in (1) intensity of the anterior pigmented border layer, (2) number of chromatophores in the stroma, (3) intensity of the pigment layer. These changes were without evidence of inflammatory process. Passow concluded then that as Horner's syndrome is dependent on a disturbance of the motor fibers of the cervical sympathetic, so heterochromia is dependent on a disturbance of the trophic-vasomotor fibers.

Of course cases of acquired heterochromia and Horner's syndrome cannot be included in this group. While Passow has shown that Horner's syndrome and heterochromia frequently occur in status dysraphicus and are a result of sympathetic paralysis due to the dysraphy, there are nevertheless cases of Horner's syndrome and heterochromia which have no relation to status dysraphicus. Paling of the iris may follow trauma, or severe inflammation, or it may be a result of the ordinary workings of senility. Likewise Horner's syndrome is not found exclusively in status dysraphicus or syringomyelia, but may occur in association with various other diseases of the cervical cord and medulla, and in various lesions of the neck. A

quite satisfactory summary of these factors is given in a recent article by DeJong³⁰

The facts so far mentioned reveal that status dysraphicus is a distinct clinical entity. It is of interest to the ophthalmologist because of the frequent occurrence of Horner's syndrome and heterochromia iridis.

The similarity of the signs and symptoms of arachnodactyly and status dysraphicus becomes apparent as soon as one becomes familiar with the two conditions. Passow²⁷ pointed out this similarity in 1935. In arachnodactyly there is an over-length of the extremities, particularly of the hands and feet. The fingers and toes are unusually long, thin and tapering. In status dysraphicus the arms are too long and the span of the extended arms is greater than the body length. The hands are usually hypertrophic but in some cases may be very gracile. Web formation of the digits, funnel thorax, anomalies of the spine, winged scapulae, highly arched palate and anomalies of the external ears are common to both syndromes.

The eye findings, however, seem to be entirely different in the two conditions. In arachnodactyly we find congenital luxation or subluxation of the crystalline lens and poor reaction of the iris to mydriatics. In status dysraphicus there are heterochromia of the iris, Horner's syndrome and occasionally cataract formation. While the analogy of most of the symptoms suggests the relation of the two complexes, the ocular findings seem to show the contrary. It is possible, however, according to Passow to bring the eye findings of the two conditions together on the same basis. As was shown in the first half of this paper it is possible to explain all the findings in arachnodactyly, including the ocular, on the basis of a mesodermal maldevelopment. In status dysraphicus, the eye findings are explained by Passow as being the result of a dysraphy of the spinal cord, producing a paralysis of both motor and trophic-vasomotor fibers of the cervical sympathetic. And he believes all the symptoms of the disease are to be explained on a similar basis. As already mentioned, Weve² always found the lens in arachnodactyly very small, and the dilator pupillae muscle undeveloped. Passow explains these defects, as well as the ocular defects of status dysraphicus on the same basis. In embryonic life the lens is surrounded by a vascular membrane, the blood supply of which arises from the long posterior ciliary arteries. A dysraphy then, says Passow, could cause Horner's syndrome through paralysis of the motor fibers of the cervical sympathetic, heterochromia through paralysis of the trophic-vasomotor fibers of the sympathetic, and microphakia and ectopia lentis through trophic vasomotor disturbance of the tunica vascularis lentis in embryonic life. Actually an atrophy of the pigment layer of the iris and persistent pupillary membrane are quite frequent findings in arachnodactyly, as already mentioned by Weve² and Igersheimer²¹. Passow showed that after experimentally produced sympathetic paralysis in young animals there occurred not only Horner's syndrome but also a dystrophy of the entire iris, the ciliary body and the zonules.

It follows that one should be able to demonstrate cases of arachnodactyly showing evidence of status dysraphicus and vice versa. In reviewing the literature we found a few such cases mentioned, but, since status dysraphicus has been known for only a relatively short time, most observers simply did not look for signs of this anomaly in their cases of arachnodactyly. Brock³¹ in his case of arachnodactyly observed acrocyanosis, funnel thorax and spina bifida. Carrau,⁷ Weber,³³ and Boerger¹³ reported cases of arachnodactyly showing funnel thorax and kyphoscoliosis. Muscular weakness was often reported and this in some cases might be construed as a symptom of status dysraphicus, especially if the muscles involved were of the spinal group. We were unable to find any case of arachnodactyly with heterochromia iridis. One case was reported, however (Boerger), which may have had a Horner's syndrome. In this case he reported that the right lid fissure was somewhat larger than the left and the right bulb more prominent. We can only hazard an opinion that what this case actually showed was a small palpebral fissure and enophthalmos of the left eye (Horner's syndrome).

Passow reports two cases of his own which strengthen his idea of the similarity of the two conditions. The first, a 14-year-old girl, had spider fingers, luxation of the lens and eccentric pupils as well as heterochromia iridis and a difference in the size of the mammae, the smaller mamma being on the side of the paler iris. The hands were moist, cold and livid; there was deformity of the spine, webbing of the fingers, highly arched palate and increased reflexes. The second case, a 20-year-old boy, had spider fingers, luxation of the lenses and a heart lesion as well as overlength of the arms and heterochromia iridis. As to other symptoms he had funnel thorax, winged scapulae, and webbed fingers.

SUMMARY

Arachnodactyly is a little known developmental disease due probably to a maldevelopment of the mesodermal derivatives. Status dysraphicus is a distinct clinical entity to be explained on the basis of a mild form of syringomyelia. There are so many characteristics typical to both arachnodactyly and status dysraphicus that there is a reasonable excuse for believing the two diseases to be identical or at least closely related from an etiological standpoint. Passow's idea of the similarity of the two diseases has so many points in its favor that further reports are desirable either to confirm or disprove the theory.

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CLINICAL MANIFESTATIONS AND STUDIES IN PARENCHYMATOUS HEPATITIS

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It is a paradoxical fact that one of the most accessible and important organs of the body, the liver, is the one about which the least is known. The multiplicity of its functions is appreciated but little understood. Therefore, for practical as well as theoretic purposes, any data concerning liver function, metabolism and pathology are deserving of record.

The baffling part of the liver problem lies in our inability to reproduce in animals conditions frequently found in man. Liver necrosis, hepatitis, cirrhosis, atrophy and regeneration have all been reproduced experimentally with varying degrees of success. These experimental lesions and their effects have been carefully studied. Yet none have been observed that satisfied every criterion. When morphologic alterations are produced, the physiologic changes may not strictly parallel those observed in man, in corresponding diseases, and vice versa.

Results approximating those seen in man have permitted simultaneous studies upon the pathologic histology and the physiologic chemistry. These studies have been carried on in animals suffering from acute or from prolonged liver damage induced by various types of hepatotoxins. In making comparisons, care must be taken in drawing conclusions, because powerful liver poisons produce disproportionate changes in different species. Furthermore, it has been shown that the previous diet of the experimental animal may, to a large degree, influence the results.

Among the many known chemical agents used to produce parenchymal liver damage, the effects of the hydrazine group have been extensively investigated. Bodansky, Underhill, Lewis and Izume have studied the action of the hydrazines upon liver metabolism in animals. They have shown that chronic intoxication with hydrazine and certain derivatives has interfered with the glycogenic function. Wells was able to show that hydrazine and its derivatives produced parenchymal injury to the liver of animals. The architectural structure of the liver was changed by early damage of the cells in the center of the lobule. The injury then extended to the periphery of the lobule, ultimately resulting in diffuse fatty changes. Wells in his early work stated that whereas other substances, such as the heavy metals, produced changes in other parenchymatous organs of the body, hydrazine limited its effects solely to the liver. Subsequent experiments have shown that this rather unique effect of hydrazine may be produced by a few other substances. In our series of animals studied thus far, acute intoxication pro-

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duced hepatic injury only. In man, however, chronic hydrazine poisoning resulted in changes in other tissues.

In addition to the histological changes in the liver parenchyma, hydrazine exercises another very important effect, namely that upon the glycogenic function of the body. Underhill and his co-workers as early as 1908 began studies of this problem. They noticed the marked hypoglycemia that results from the administration of hydrazine sulphate. This reduction in blood sugar was accompanied by an almost total disappearance of glycogen from the liver and from the muscles of the body. Underhill could offer no explanation for this effect. Bodansky, using the levulose tolerance test as a measure of hepatic injury, carried on extensive investigations of the variations in degree of liver damage produced by hydrazine and by certain hydrazine derivatives. His observations, which agreed with those of Wells, indicated that hydrazine sulphate produces fatty degeneration of the liver with almost complete disintegration of the hepatic cell without much apparent damage to other organs of the body. However, more complicated hydrazine derivatives and notably phenylhydrazine, when given to the experimental animal in quantities sufficient to cause "liver death," produced early changes in other organs of the body, notably in the kidneys, the spleen, and the bone marrow. He concluded that the hydrazine group constituted a powerful protoplasmic poison that acted chiefly upon the liver and seriously interfered with its glycogenic function.

Later, Izume and Lewis investigated the entire subject again. They concluded that hydrazine not only prevents the transformation of non-carbohydrate material into glucose and glycogen, but also prevents the synthesis of glycogen from glucose. This interference with glycogenesis interrupts the process of storage of glycogen in the liver. As a result the muscles are starved owing to the inability of the body to mobilize glycogen for their use. This condition is identical with that which Mann and his co-workers described in the completely hepatectomized animal. Intoxication with hydrazine and its derivatives results in a failure on the part of the body to form glycogen from glucose, from protein derivatives, and from fatty acids. That the synthesis of lactic acid is prevented also seems probable.

It was my good fortune to have the opportunity of studying the effects of a chemical compound from which hydrazine may be derived on two men exposed to the vapor of a nitrosamine. These two patients had repeatedly inhaled this chemical poison in sufficient amounts to produce headache, backache, abdominal cramps, nausea, anorexia, weakness, drowsiness and giddiness. They were poisoned in a rather unusual manner. Both were engaged as chemists in the production of dimethylnitrosamine to be used as an inhibitor for the prevention of corrosion. Their contact with this chemical substance was chiefly by inhalation. The first patient was assigned to the task of development and manufacture of dimethylnitrosamine. While engaged in this he became ill and could not continue his work. He

left the employ of the company for the purpose of seeking medical aid. It was approximately 16 months later that the second man was assigned to resume the production of the substance, at the point where the first chemist stopped. It was not until the second man developed symptoms and signs identical with those observed in the previous case, that the cause of these symptoms was suspected. The second man's intoxication followed repeated inhalations and the wiping up of a quantity of the substance that was accidentally spilled on the floor. He was the more severely affected of the two and died following an exploratory operation. Others who had worked in the same laboratory and had more or less contact with the suspected chemical substance were interviewed. All of them gave some history of dizziness, faintness, headache and weakness.

CASE REPORTS

Case 1 T. C., chemist, aged 29, single. The chief complaints are pain in the upper right quadrant, nausea, a sensation of weakness in the upper abdomen, and occasional abdominal cramps. He had cerebro-spinal meningitis at one year, and pneumonia and pleurisy at seven years. In 1925 he sustained an injury to one of his cervical vertebrae. In 1932 he suffered from what was diagnosed as "colitis" and anal fissure. He dates the beginning of his present illness to about July 1933, at which time he was engaged in the making of dimethylnitrosamine for commercial use. It was during the development of this synthetic compound that he began to feel ill. The patient states that on August 2, 1933, after he had been exposed daily to the fumes of this substance, he began to believe that the inhalation of it was making him ill, and he reported the fact to the company physician on that day. However, he continued to work irregularly up to August 15, when he felt so ill that he decided to quit. He complained of exhaustion, headache, cramps in his abdomen, deep soreness in his left side, nausea, some vomiting, occasional backache and utter fatigue. August 16 he noticed that his abdomen was distended and reported it to his physician who sent him into the hospital for further observation. On August 20 a paracentesis was performed and about two and a half quarts of fluid were withdrawn. Although the abdomen slowly filled again, no further tapping was resorted to. The patient states that he was told that he had "peritonitis," and that it probably was tuberculous in origin. He entered a sanatorium in Newburg, N. Y. Although he remained distended for some time no further paracentesis was performed. He remained in the tuberculosis sanatorium until January 1934, at which time he was discharged. Careful examination revealed no evidence of tuberculosis and the patient was returned to his home where he sought further medical advice because of the persistence of headaches, abdominal pain, and weakness. He remained in bed at his home until April 16, 1934, and then left to consult physicians in a large clinic in a hospital in New York City. He was thoroughly examined but nothing was found. A submucous resection was advised and was performed on May 25, 1934. He returned home to a small town in New York State, with instructions to rest. He rested all summer, enjoying a maximum of sunshine. Gradually the attacks of pain became less frequent. The patient states that he was jaundiced at the beginning of his illness. He also thinks that he had a short period of jaundice in the early part of January 1935. He is sure that he never had any fever. He has slowly regained his weight, which at one time he believes was about twenty pounds under his average. He admits that the entire illness has made him somewhat nervous and depressed. There is no history of clay colored stools. He does not remember passing dark urine.

His habits are good. He rarely takes alcohol. Smoked very little prior to 1933 and not at all since. He is a moderate eater. There is no history of tuberculosis, cirrhosis, or of any degenerative diseases in his family. His parents and brothers are all living and well.

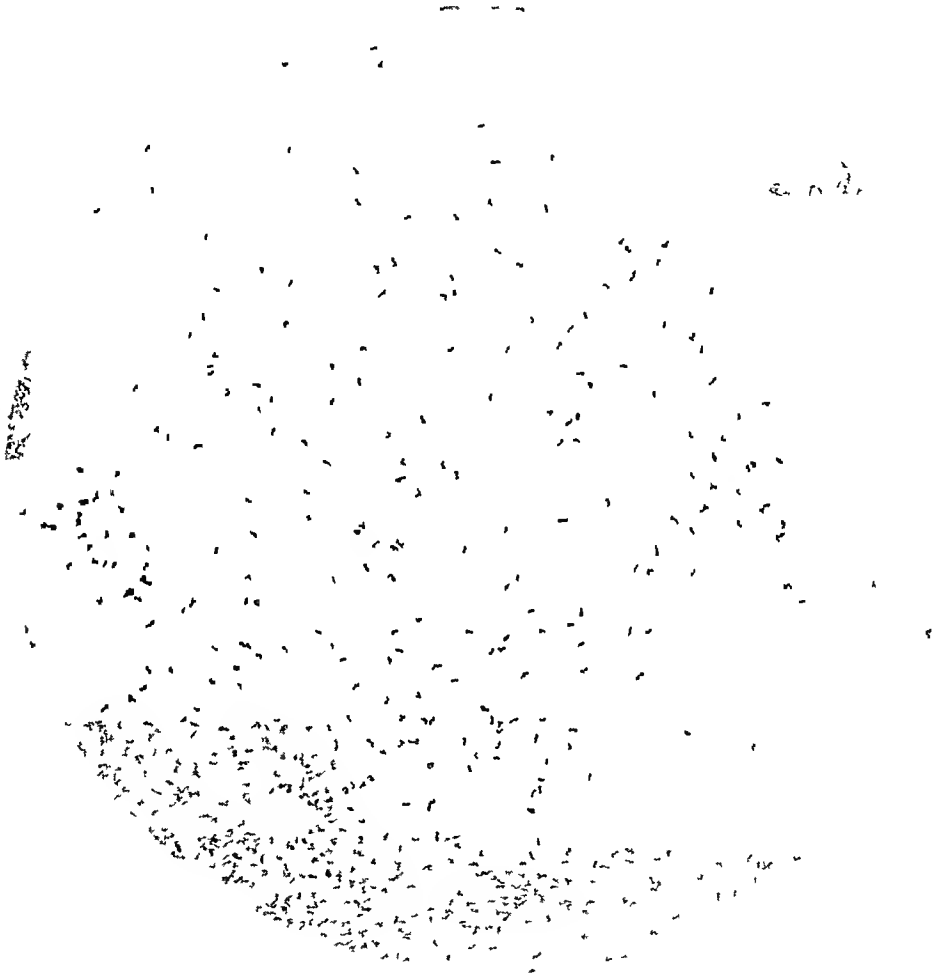


FIG 1 Diffuse liver injury with multiple miliary hemorrhages

Physical examination reveals nothing of importance about his head, neck or chest. Blood pressure 132 systolic and 68 diastolic. His abdomen is slightly above the level of his ribs, and shows a moderate panniculus. There is tenderness throughout the whole abdomen on light palpation, especially in the right upper quadrant where there is definite muscle spasm. The liver is felt two fingers-breadth below the margin of the ribs, it is moderately firm and tender. The spleen is not felt. All reflexes and tests of sensation are normal. The non-protein nitrogen is 40 mg per cent. Blood sugar taken in the middle of the afternoon, after his noon day meal, was 66 mg per cent. Kahn test negative.

The patient promised to return for more study, but was not seen again until February 17, 1936, when he entered Harper Hospital. Physical examination at this time did not differ from the one made eleven months before. Studies of his blood and blood chemistry on this occasion were as follows:

Blood Count Hgb (Newcomer) 84 per cent Erythrocytes 3,680,000 Leukocytes 7,000 Color Index 11 Reticulocytes 1 per cent Thrombocytes 349,400 Differential Count Metamyelocytes 3 per cent, neutrophiles, stab 20 per cent, neutrophiles, segm 26 per cent, eosinophiles 0, basophiles 1 per cent, total of granulocytes 50 per cent, lymphocytes 48 per cent, monocytes 2 per cent

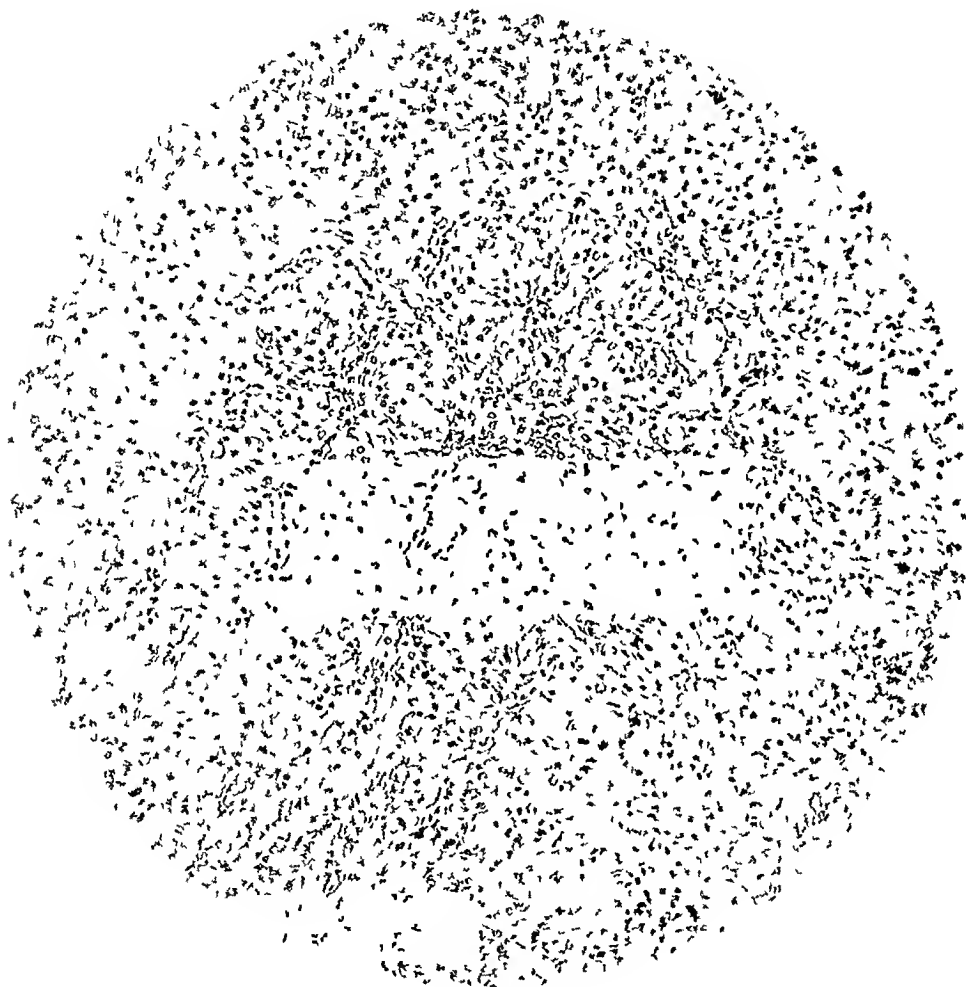


FIG 2 Acute intoxication with liver cell destruction Hyperchromatic and pyknotic nuclear changes

Urinalysis Fresh specimen color yellow, reaction acid, sp gr 1.015, albumin 0, sugar 0, urobilin 0, acetone 0, diacetic 0, bile 0 Phenolsulphonephthalein test Normal output and curve Non-protein nitrogen 30.9 mg per cent, icteric index 8, calcium 10 mg per cent, phosphorus 2 mg per cent Van den Bergh Direct, negative, indirect, slightly positive Takata-Ara test, negative Albumin-globulin ratio 9.43/4.95 Numerous blood sugar tolerance curves were done, all of which showed an increased tolerance Bromsulphalein test showed normal maximal dye elimination Kahn test negative Basal metabolic rate plus one Gastrointestinal roentgenograms revealed no abnormal findings Cholecystography revealed a normally functioning gall-bladder

During the patient's hospitalization, the pulse rate averaged 80 There was no elevation of temperature

Case 2 H B, aged 26, white, single, chemist, complains of pain in his abdomen, weakness, lack of appetite and headache He dates the beginning of his illness from December 1, 1934, at which time he began working on the job of pro-

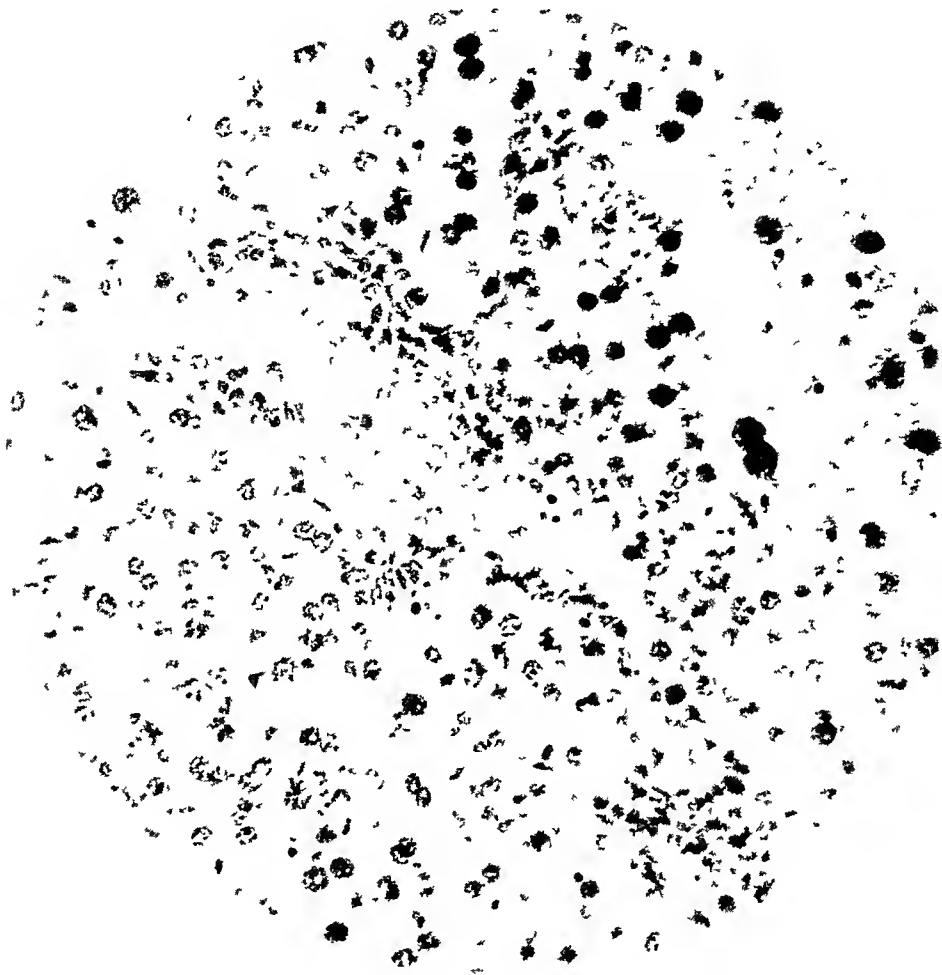


FIG 3 Diffuse parenchymal injury showing nuclear changes in liver cells, mitoses, beginning leukocytic infiltration and thromboses in the small veins

ducing nitrosamine On December 12, 1934, he dropped a flask containing about one liter of this substance, spilling the contents He used an ordinary mop and rag to clean up the fluid He was very ill that night and the next day unable to return to work About December 18 he began to have pain in his upper abdomen, cramps and a feeling of distention He became constipated About December 20 his abdomen became more tender and the distention grew progressively worse There was a marked loss of appetite, slight nausea, but no vomiting He is uncertain as to the time that his skin became yellow, but believes that it began simultaneously with the enlargement of his abdomen His past history is unimportant There is no previous record of respiratory, cardiac, renal or gastrointestinal diseases He smokes 20

cigarettes per day, rarely uses alcohol. There is no history of cirrhosis, cardiac renal or vascular disease in his family. He entered the hospital on December 26, 1934.

Physical examination revealed an acutely ill patient, lying quietly in bed, pale and somewhat emaciated. The sclerae were slightly icteric, examination of the head was otherwise negative. Examination of the lungs revealed signs of free fluid in each pleural cavity. The heart was not enlarged, the heart sounds were clear and of good quality. Blood pressure 120 systolic and 76 diastolic. Nothing noteworthy was found about the peripheral vessels. The abdomen was distended and showed bulging on both sides. There was no visible venous engorgement. Both shifting dullness and a fluid wave were present. The abdomen was not rigid. The margin of the liver could be felt on palpation about three fingers below the right costal edge. It was tender. No other organs or masses were palpable. The genitalia were normal, no masses felt in the testes. Prostate and seminal vesicles normal.

On December 28 abdominal paracentesis was performed and 3,500 c.c. of fluid removed. Paracentesis was performed three times afterwards, at about one day intervals, 6,000 c.c. was the largest amount removed. Two c.c. of salyrgan were given intravenously daily for five days beginning January 10. At no time did the temperature rise above 99.2°. The pulse varied between 80 and 100, and the respirations between 20 and 26. I saw the patient in consultation on January 20. My examination confirmed the previous findings in all respects. On the following day paracentesis was again performed and 5,000 c.c. of fluid obtained.

Laboratory Findings Urinalysis (Jan 4, 1935) Fresh specimen, amber, clear, acid, sp. gr. 1.022, albumin trace, sugar negative, acetone negative, occasional hyaline cast, occasional pus cell, no red blood cells. Blood count (Jan 24) Hgb 80 per cent, erythrocytes 4,600,000, leukocytes 9,900, polynuclears 72 per cent, small lymphocytes 28 per cent, some variation in the shape and size of the red blood cells. Blood chemistry (December 28, 1934) Icteric index 16, van den Bergh reaction, faintly positive, direct and indirect. Kahn test negative. Roentgenogram of chest (Dec 27, 1934) Slight elevation of the right diaphragm. There is apparently a pneumonitis in the right base. Fluoroscopic examination shows movement of the right diaphragm. The remainder of both lung fields is clear. There is no evidence of pulmonary tuberculosis. Examination of ascitic fluid Sp. gr. 1.010, Wright's stain of centrifugated fluid showed a few red blood cells, and 61 per cent polynuclears and 39 per cent lymphocytes. Kahn test negative. Non-protein nitrogen 22.2 mg. per cent. Albumin 0.35 grams, globulin 0.38 grams, fibrinogen negative. Total protein 0.73 grams. Calcium 9.78 mg., phosphorus 3.55 mg., cholesterol, faint trace present. An exploratory laparotomy was performed. Summary of data recorded by surgeon: "Large amount of yellowish ascitic fluid. Liver extremely engorged, about a hand's breadth below margin of rib, smooth and purplish in color. Spleen markedly engorged and lobulated, purplish in color. Gall-bladder and duct somewhat thickened, no stones, emptied readily. Omentum retracted with many adhesions to the abdominal viscera. Appendix buried in a mass of adhesions. The pancreas appeared normal. The peritoneum and the mesentery were smooth and not injected. No tubercles were seen. The patient stood the operation poorly." He died on January 28.

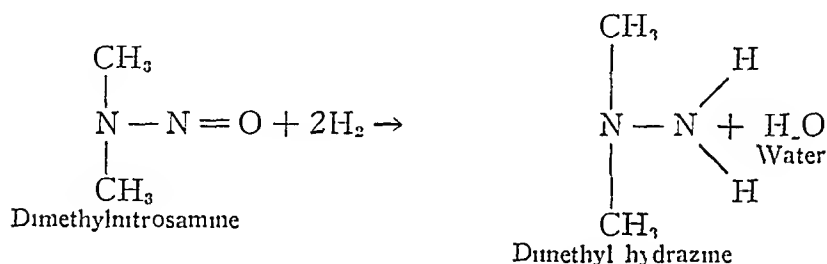
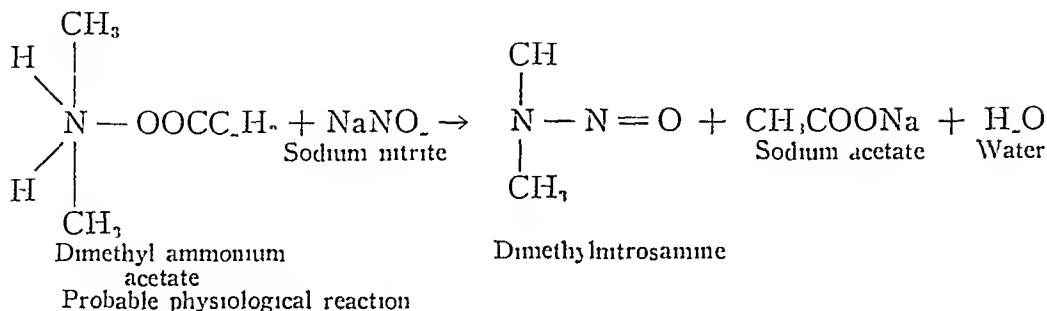
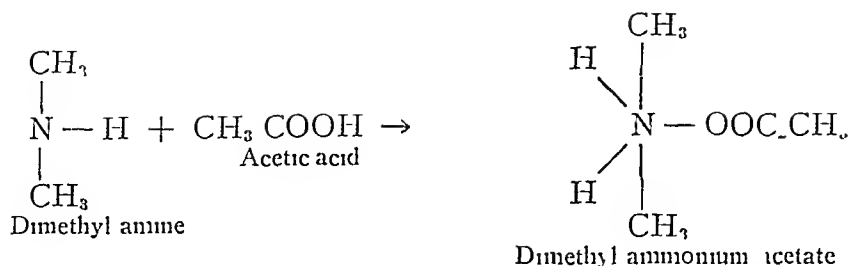
Autopsy I am indebted to Dr. Lewis for the following notes. (Only data bearing on the condition are recorded.) Postmortem suffocation is extreme. Rigor mortis is marked throughout entire body. Conjunctivae, sclerae and the skin are slightly jaundiced. Superficial lymph glands are palpable. Right pleural cavity contains about 400 c.c. of serous fluid. Left pleural cavity contains about 100 c.c. of blood stained serous fluid. The pleural surfaces are everywhere smooth and glistening. The pericardium contains a slight excess of pericardial fluid. There are a

number of small subpericardial hemorrhages. The heart weighs 230 grams. The myocardium is light brown in color, very soft and flabby. There is dark blood in all the chambers, no agonal clots. Lungs. The right lung weighs 290 grams. The left lung weighs 320 grams. The left lower lobe is dark red, firm in consistency. There are small hemorrhages in the bronchi and trachea. The spleen weighs 320 grams. It is extremely soft. The pulp is uniform, mushy in consistence and rather darker than normal. There are some adhesions and some fibrinous exudate over the upper portion of the spleen. The gall-bladder contains about 20 c.c. of dark greenish-brown viscous bile. The biliary channels are patent. The liver weighs 1,380 grams. It is dark, greenish, mottled brown, rather firm in consistence. On section it presents a definite, greenish-brown, mottled appearance. The stomach is somewhat dilated. The mucous surface is thickened and the rugae are deep. In the prepyloric region there are numerous superficial hemorrhages and one small superficial ulceration, measuring 2 cm. at its greatest diameter. The duodenum, the jejunum, and the small bowel are not remarkable. The mesenteric lymph glands are markedly enlarged, and very pale and pinkish in color. The lower portion of the ileum is thickened. Its serous surface is covered by a firm, fibrinous exudate. There are occasional superficial hemorrhages scattered throughout the entire mucous surface of the small bowel. The appendix is long, retrocecal and covered by old adhesions. The adrenals are not remarkable. Kidneys. Combined weight of the kidneys is 300 grams. They are dark brown in color, the capsule is thickened and is fairly adherent to the underlying cortex. On section the renal markings are not well defined. Bladder and prostate reveal nothing abnormal. Summary of microscopic findings (P. S. Morse). Liver. Acute diffuse degeneration of the whole parenchyma with focal and diffuse areas of necrosis. The necrotic areas are infiltrated with round cells and phagocytes. Multiple periportaliliary hemorrhages. Areas of intense regenerative proliferation of liver cells with marked irregularity in size and staining reaction of protoplasm and nuclei. Kidney. Acute terminal passive congestion. Glomeruli and tubules normal. Some bile retention in tubules. Small intestines. Marked proliferative productive peritonitis. Thickening, edema and round cell infiltration of peritoneal coat. Heart muscle. Virtually normal, slight edema, no hypertrophy or muscle cell destruction, no fatty infiltration. Suprarenals. Normal cortex and medulla, no necrosis, no adenomatous zone, no small cell infiltration. Spleen. Postmortem autolysis, no cellular changes. Lymph nodes. Diffuse fibrosis, increase in size of coarse trabeculae, edema of gland as a whole, scarcity of germ centers. Bone marrow. Red marrow shows usual myeloid picture.

ANIMAL EXPERIMENTS

The nitrosamines have not been extensively used in industry. Manufacturers of the chemical had no occasion to suspect that its use, much less its inhalation, was fraught with danger. It is a clear yellow liquid soluble in alcohol, of surface tension one-sixth that of water. It has a slightly pungent, though not unpleasant odor. It is not particularly irritating to the mucous membranes. It has no corrosive action when applied to the skin.

In this instance it was intended for commercial use as an inhibitor of corrosion and a stabilizer. In the process of manufacture the following chemical steps took place:



As I was unfamiliar with the toxicity of dimethylnitrosamine and the literature contains no data bearing on the subject, it was decided to study the effects first upon mice, and later upon larger animals. A white mouse was placed in a one-liter jar, to the lid of which was fastened a gauze screen, saturated with 10 c.c. of dimethylnitrosamine. The jar was not sealed, a small amount of air being allowed to enter at the top. The immediate effect of the substance was irritation of the eyes, nose and skin, although the reaction did not seem to be a violent one. The respirations were not apparently affected. In a short time the mouse appeared sick and remained quiet. In 18 hours, mice subjected to one-half hour exposure to the fumes died in convulsions. Autopsy of such mice revealed nothing unusual on gross examination. There was perhaps slight injection of the peritoneum, some reddening of the bronchial mucosa. On microscopic examination the liver was the only tissue affected. There was diffuse regenerative hypertrophy and proliferation of liver cells. There was marked variation in shape and size and staining qualities of the nuclei of the liver cells. Marked irregularity of chromatin distribution was observed with pyknosis and autolysis.

A dog, weighing 12 kilos, was placed in a box and a small amount of air was permitted to enter. Gauze saturated with 30 c.c. of dimethylnitro-

samine was fastened to the lid of the box. The animal was kept in this chamber for 30 minutes. Except for occasional sneezing the animal did not seem to be irritated by the fumes of the substance. He was happy when removed from the box and showed no ill effects from the fumes. Eighteen hours later the dog had a mild convulsion. His blood sugar at that time was too low to read. Intravenous glucose was administered. Although the animal recovered slightly, it was impossible despite continued intravenous administration of glucose to influence the constant twitching. The blood sugar level could not be brought up to normal. The dog died in hypoglycemic shock. At autopsy gross examination revealed nothing abnormal in any of the tissues of the chest or abdominal cavity. Blood removed from the heart revealed no methemoglobin. Microscopic examination. The liver showed acute diffuse degenerative changes, evidenced by necrosis, especially in the region of the central vein with marked shrinking and acute atrophy of liver cells at the periphery of the lobule. This process had led to an enormous apparent widening of the bile capillaries. In the necrotic areas infiltration of phagocytes and phagocytosis had barely begun. Many liver cells had lost their staining quality in atrophic areas. Only the nuclei took the stain. Lungs. Acute diffuse pulmonary edema with acute terminal passive congestion. Relative atelectasis. The larger bronchi were filled with mucus and desquamated epithelium. Heart. Normal throughout.

A second dog weighing 10.5 kilos, was then subjected to inhalations of 10 c.c. of dimethylnitrosamine for a period of five minutes daily in the same chamber. The animal did not seem irritated by the exposure. On the fourth day the dog appeared less active than he had been previously. He played about, however, fairly well. On the fifth and last day that the dog was subjected to the inhalations he seemed less active. On the sixth day the sclerae and mucous membranes were distinctly jaundiced. The urine contained a moderate amount of bile. The dog drank glucose and water freely, but refused to eat. On the seventh day the animal twitched occasionally. There was no spasticity. Vomitus of clear fluid on two occasions. The gait was somewhat unsteady but there was no paralysis.

Autopsy. There were no abnormal findings in the gross examination. Microscopic findings. The liver showed uniformly distributed diffuse hemorrhages around the central veins, which extended peripherally and did not involve the portal area. No changes were noted in the pancreas, spleen, suprarenals, kidneys and heart muscle.

Experimental cirrhosis resulting from hepatic injury has been produced in many ways. Moon has completely reviewed this subject. Of all the hydrazines only phenylhydrazine is used in the practice of medicine. Its pharmacologic action is well understood and differs greatly from that of many hydrazine salts. Hurst and Hurst were able to produce cirrhosis with ascites by the simultaneous administration of hydrazine sulphate and manganese dioxide. In their animals a diffuse parenchymal destruction took

place involving the entire liver lobule which differed histologically from the effects of dimethylnitrosamine.

In all likelihood this difference is due to the fact that dimethylnitrosamine is carried by the arterial blood to the liver cell where it exerts at least a twofold action, firstly it causes liver cell destruction and secondly it is glycogenolytic. In this respect it differs from other hepatotoxins that have been studied, and by the same token it affords another method of approach to the study of liver problems.

SUMMARY

The chief points in our knowledge of the toxic parenchymatous hepatitis due to dimethylnitrosamine may be summarized as follows:

1. Dimethylnitrosamine is a volatile toxic substance which upon inhalation exerts a destructive action on the liver. Its use should be considered as an industrial hazard. Its immediate and remote toxicological effects have been described. It probably is reduced in the liver to a hydrazine and acts in that form.

2. The primary seat of action is about the center of the liver lobule where it produces a degenerative necrosis of the liver cell. Continued and more intensive poisoning results in the destruction of all liver cells. Ultimately partial bile duct obstruction takes place.

3. Dimethylnitrosamine destroys the glycogenic function of the liver. Hypoglycemic shock, in all respects resembling that seen in the hepatectomized dog, may be produced with dimethylnitrosamine. When recovery takes place, glycogenesis is impaired. Muscle glycogen reserve is diminished.

4. Two human cases are reported of toxic parenchymatous hepatitis with ascites, due to poisoning with dimethylnitrosamine. Toxic portal cirrhosis with ascites may be experimentally produced with dimethylnitrosamine.

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PAIN AND PAIN EQUIVALENTS IN HEART DISEASE

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APPROXIMATELY 90 per cent of all non-traumatic sudden deaths are cardiovascular in origin, and 65 per cent are due to coronary artery disorders. A study of these cases of sudden death demonstrates a strikingly large number who gave a history of precordial or near-by pain preceding or during the fatal illness. The majority of these show pathological evidence of antecedent changes in the coronary vessels—namely sclerosis, but these changes were not the cause of death. Some added mechanism caused a sudden cardiac standstill.

This tragic event—sudden cardiac death—is well known even to the laity, but the symptoms leading up to it are not so well known, nor is it sufficiently recognized that practically all of the earlier symptoms may be encountered in disorders not at all associated with the cardiovascular system. Of these early evidences of coronary disorder, pain is both numerically and psychically the most important manifestation. Because of this frequency of pain and its effect upon the patient's morale, a consideration of the various types of cardiac pain, their origin and distribution and associated symptoms and signs will be presented, and an attempt made to differentiate pains which are a manifestation of cardiac disorder from those arising from other tissues, and tending to cause diagnostic confusion.

At a period when anatomical changes occupied the center of the medical stage and before disturbed physiology was seriously considered as a cause of disease processes, Heberden in 1768, under the title "Some Account of a Disorder of the Breast," gave the first clear description of the condition since known as angina pectoris. He stressed the importance of nervous and mental influences and stated that this condition belongs to the class of the spasmodic, rather than that of the inflammatory complaints. Throughout the history of this disease it seems apparent that medical men are peculiarly susceptible to it. John Hunter recognized the rôle of emotional strain and wrote that his life was in the hands of any rascal who chose to annoy him. He died in a fit of temper. But that emotional strain was not the sole factor was suggested by Jenner in 1799 when he described the frequent association of angina with disease of the coronary arteries. Three years before he had seen Hunter in his second attack and suggested in a letter to Heberden this probable association.

It was not until about 50 years after Heberden's first article that Reeder (1821) suggested that many other conditions might produce a type of precordial pain sufficiently similar to justify the use of the term "pseudo-angina." From this period until the latter part of the last century there was

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little added until the writings of Mackenzie, Allbutt, Wenckebach, and Osler, who in 1897 stated that angina pectoris is "not a disease but a syndrome or symptom complex" Sir Clifford Allbutt, in a letter to Dr Robert L. Levy¹ gave his last definition of angina pectoris "Angina pectoris is a pain, sometimes slight, sometimes agonizing, arising usually under the sternum and referred in certain definite directions, due to stretching of the outer coat of a morbid aorta, or in a few cases of that of the heart itself This is my first hasty suggestion for your 'definition'"

In late years the term pseudo-angina has largely been discarded, although as recently as five years ago Harlow Brooks² used it to designate a condition "where anatomic defects do not exist in the heart or aorta, whereas in true angina pectoris I hold that lesions exist to a recognizable degree in practically all instances" He believed that most patients with pseudo-angina were neurotics, but appears not to have taken into account the existence of a significant number of instances of true angina pectoris in which neither physical nor electrocardiographic examination reveals unequivocal evidence of heart disease Current writers employ the terms angina pectoris and anginal syndrome synonymously, although the present tendency is to modify the latter with a qualifying phrase as to etiology

Throughout this later period there have been three main theories of pain production in the heart Allbutt believed that the pain arises in aortic lesions mainly Opposed to this was the teaching of Mackenzie that the pain was due to exhaustion of the myocardium induced by coronary artery disease Closely related to this was the theory of Allan Burns who in 1809 attributed the pain to anemia of the heart muscle Sigler³ recently shows that the carotid sinus reflex is increased in the vagotonic individual and suggests that resultant coronary vasoconstriction and myocardial ischemia may be the cause of angina At the present time, the majority of workers consider ischemia of the heart muscle as the most acceptable cause of angina pectoris But that this is not the sole cause was shown by Katz⁴ recently While bodily exercise and generalized anoxemia may precipitate attacks in patients subject to anginal seizures—usually with rather characteristic alterations in the electrocardiogram, which are similar to those occurring in spontaneous attacks—Katz⁴ has demonstrated that similar ischemic changes may be experimentally produced in normal persons without causing precordial pain, which observation leads this author to conclude that some other factor than ischemia plays an important rôle In animal experiments Katz shows that "Continuous pain can be produced in contracting skeletal muscle when the muscle is rendered ischemic", that in the dog "Pain response was not due to the occlusion of the coronary artery, but to stimulation of afferent pain fibers located in the nerve plexus surrounding the vessels" He concludes "The stimulus for pain appears to consist of some metabolic product produced quantitatively in proportion to the work done by the heart The amount of the product produced is increased when the heart works ineffi-

ciently, especially when the diastolic blood pressure is elevated, because the heart has to exert more effort in raising the pressure of its contents above the diastolic aortic pressure "

Evidence ⁵ derived from experimental arrest of the circulation of the human limb, carried out with and without associated effort, seems to justify the belief that whenever, in the presence of sclerosis or other coronary artery obstruction, the work of the heart is so increased that the demands upon the coronary circulation exceed the vessel capacity—anginal pain ensues. These experiments showed likewise that fatigued muscles failed to exhibit pain under similar conditions, suggesting an explanation for the clinical observation that the failing heart muscle is rarely associated with anginal attacks.

Thomas McCrae ⁶ challenged the idea that angina pectoris is always due to coronary disease and believed that we should regard this disease as one having a multiple etiology, including myocardial disease, viscerosensory reflexes, and possibly purely neuro-psychic mechanisms. It is certain, at least, that extra-cardiac factors precipitate attacks. Early gastric lavage prevented attacks in one patient, in another prostatic treatment "cured" the angina. I have in mind also a man whose anginal attacks were relieved for a period of many months following a cholecystectomy, yet later he again suffered from angina and died in his second attack of coronary thrombosis.

In a very recent report ⁷ experimental and clinical evidence is presented in support of the statement that "Angina pectoris is due to acute, spasmodic, incoordinated contractions of the esophagus and stomach." Dr. Jackson's presentation of this subject at the Kansas City meeting of the American Medical Association was quite convincing, but corroboration must be forthcoming before such a novel theory can attract more than passing interest.

Warthin ⁸ taught that syphilis plays an important rôle in the causation of atherosclerosis, hence that coronary thrombosis and angina pectoris occur more frequently in syphilitics. To all of Warthin's students it was well known that he found evidence of syphilis where his contemporaries were unable to satisfy themselves as to its occurrence. Scott ⁹ also found one-half the cases of coronary artery disease dependent upon syphilis. Others do not find that syphilis predisposes to coronary sclerosis. Certainly present day teaching ¹⁰ does not stress syphilis as a cause of angina pectoris. The race in this country most extensively invaded by syphilis, the negro, shows a notable freedom from the anginal syndrome. Roberts ¹¹ of Atlanta offers as an explanation of this fact that the negro "never worries very long about any one thing at any one time," and suggests that "the white man's burden is his nervous system." An English physician, Donnison, ¹² who had a considerable experience in the Orient, stated that he had never seen angina pectoris in natives in Central Asia or China. An inquiry directed to a physician of 40 years' experience in India corroborates this observation. Wenckebach ¹³ noted as early as 1904 the marked difference in the incidence

of angina pectoris among a rural population as compared to that of the cities, but when he went to Vienna he observed a marked increase in these cases in his practice, and also that there was a further significant increase in the years of and after the War, which increase he attributed to worry and strain.

It is probable that the presence or absence of the anginal syndrome is to a considerable extent dependent upon the degree to which the nervous system of the individual is sensitive to various influences, physical and psychic, for it has been amply proved that extensive limitation of the coronary circulation may exist without pain or other evidence of the anginal syndrome. It may be assumed that such individuals have a high threshold of sensitivity to those influences which act as a "trigger mechanism" and set off the painful attack in susceptible individuals. There is some evidence that this "trigger mechanism" is associated with an endocrine imbalance, since adrenalin is known to precipitate attacks in individuals subject to angina and not in controls.

It appears that there is no constant toxic or degenerative etiology, and that angina pectoris must be looked upon as the result of a combination of reactions in the nervous and circulatory systems induced in certain individuals by the stress and strain of life. In general, angina pectoris is noted in the aggressive, head of the procession, stocky individual, rather than in the neuro-circulatory under-nourished type.

Until fairly recently angina pectoris was considered, if not definitely as a disease of the intelligentsia, certainly as a disease of the upper classes, but even this idea is losing ground. Many¹⁰ doubt the importance of occupation. It has been pointed out¹⁴ that while "occupation does not appear to play a significant part in determining those whose coronary arteries are affected by sclerosis—with respect to the occurrence of pain, however, occupation seems to be of real importance," and that pain occurs in a significantly higher percentage of housewives and manual laborers than in clerical, skilled workers and professional men. These conclusions are drawn from pathological records of the Presbyterian Hospital of New York City where the women occupying the ward beds are usually of the hard working class. Probably, records drawn from groups more fortunately situated may not agree on this point. It is notable that the former predominance of males is diminishing, probably due to entrance of women into the stress of industrial, business and professional life.

Several writers have suggested that the "heart mindedness" of the laity during the past two decades may play an important part in the apparent increase in the various manifestations of coronary artery disease. This may be a factor in the increased frequency of precordial pain, but it seems more probable that the mode of life of the past two generations has led to a progressive increase in vascular degeneration, especially of the coronary vessels—to quote Osler "in the make-up of the machine, bad material was used for the tubing," and with the increased strain of the past two decades

the "tubing" is inadequate to the strain. Most of us are aware of families showing this type of defective "tubing." But in the members of such families in whom we encounter pain as a presenting symptom, we will almost invariably find excess strain of some type as a precipitating cause of the painful attacks.

The mechanism of the pain production in these cases has been the subject of numerous essays, the majority favor the view that in some manner a transient ischemia of the heart muscle occurs. In occlusion of the artery, either slowly produced or by sudden thrombosis, there is no question as to the production of anoxemia, but whether in the paroxysmal transient attacks of precordial pain coronary spasm occurs is an unsettled question, although it seems the most reasonable explanation. That disturbed metabolism may be a factor in the induction of spasm is established by the work of Blumgart¹⁵ and his associates. These authors have reported a significant number of instances of complete relief of pain in angina pectoris following total thyroidectomy. Beach¹⁶ and others have noted similar relief following subtotal thyroidectomy. It is conceivable that a vagus pressure mechanism is present in some of these thyroid cases, but it is usually conceded that the lowering of metabolic rate, and hence of the circulatory demands of the body, is the basis of the improvement.

The question is often raised why heart pain is not felt in the heart. The answer entails an intimate knowledge of the visceral nerve supply. Ordinarily painful sensations do not arise in the heart, therefore, the brain is not accustomed to recognizing heart pain, hence when an adequate stimulus occurs the pain is frequently registered as from some other body area. The factor of spread of impulse has to be taken into consideration, since in many instances of excessive heart pain there is an overflow to adjacent areas. Less readily understood is the mechanism involved in those anginal cases in which the pain is first appreciated at some point well removed from the heart, whence it is transmitted to or towards the heart—a reverse radiation process.

AGE AT WHICH THE ANGINAL SYNDROME APPEARS

Most cases of angina occur after 50, but there is ample evidence that childhood and early adult life are not exempt. Heberden had one case at two years. There exist reports of a seven weeks infant¹⁷ which died suddenly and at autopsy showed advanced degenerative coronary changes, and of a 13 year old girl whose left ventricle ruptured due to advanced coronary sclerosis. There is evidence¹⁸ that coronary narrowing may be a sequel of acute rheumatic carditis and manifest itself as early as the second decade, and that these patients not infrequently suffer from severe and typical anginal pain. There are numerous instances in the third and fourth decades.

An associated study of importance in this connection is that of the pathology of coronary sclerosis.

Leary¹⁹ has demonstrated this change as early as the third day of life, and finds it is "not rare in the first decade, more common in the second with fatal thrombosis in the third and later decades" He believes that "Atherosclerosis is a disease and not the inevitable consequence of age," and that it is due to a disturbance in the cholesterol metabolism

RELATIONSHIP BETWEEN ANGINA PECTORIS AND CORONARY THROMBOSIS

In patients with coronary artery disease angina is apt to follow strain, physical or emotional, whereas when coronary thrombosis occurs its onset is often while the patient is at rest Certain instances of angina occurring during sleep may be the result of strain during a night-mare Either type of seizure may occur with or following meals, a reflex effect that is not understood Leuten²⁰ reports two instances of coronary thrombosis which followed closely upon the taking of a cold drink In such cases there are two possibilities, a reflex coronary constriction with sequential thrombosis or a direct effect of cold upon the heart Several workers have demonstrated changes in the T-wave of the electrocardiogram following the ingestion of cold water, but in these instances there was a considerable amount of water taken which may have caused an axis shift capable of producing similar changes in the T-wave

Anginal seizures preceded the final occlusion in 22.4 per cent of 370 cases of coronary thrombosis, and in 45.1 per cent persisted or appeared after the occlusion²¹ These figures appear to disprove the earlier idea that anginal attacks are not observed following occlusion It is probable that the temporary muscle failure sequential to the infarct causes the disappearance of the former painful attacks, but with recovery these may be renewed

No attempt will be made to differentiate the type and reference of pain occurring in angina and in coronary thrombosis The diagnosis rests in part upon the antecedent history, the occurrence of preceding similar attacks, especially in angina, and the presence or absence of a strain factor, but in each the immediate pain may be identical in type, in point of origin and in distribution It is the sequence of events which tells one whether this attack is a recurrence of angina pectoris or a new situation to be dealt with—coronary thrombosis Various authors have differentiated cases by the occurrence of high or low substernal pain and the reference of this pain to one or both arms The writer is unable to make such a differentiation Likewise, there is too often an absence of the crushing, tearing, agonizing pain of the classical textbook description When this picture occurs diagnosis is made easier, but because in either angina pectoris or coronary thrombosis the pain may be mild or absent, or may originate at a point apparently not related to the heart, or may not be referred to either arm and even not transmitted beyond its point of origin—because of this variation in symptomatology, some consideration of those symptoms which may take the place of pain and their importance in diagnosis is in order

Usually the anginal patient during the short attack remains quiet, rarely even moaning, there are no theatrics, as so often noted in the cardio-neurotic who complains of pain. After the attack is over he tells of his pain. The observer is keenly aware that momentarily the patient is in agony. While the attack is ordinarily immobilizing, that is, the patient "stops in his tracks," there are some who continue walking at a slower pace with relief. I have under my care at the present a man of 69 years who has frequent attacks (I have seen him in one severe seizure), and whose greatest relief comes with slowly pacing around his room. Wenckebach²² compares this with "second wind," a physiological phenomenon of which we know remarkably little. Contrast both of the foregoing with the restless and panicky seizure associated with tobacco sensitiveness.

As a rule, the anginal attacks are of short duration—a few minutes, very rarely 15 to 30 minutes, a point of differentiation between angina pectoris and coronary thrombosis, for in the latter the pain continues until relieved by morphine, unless of the very mild or painless type. In both conditions the pain is uninterrupted, though there may be slight changes of intensity which are not dependent upon drugs. On the other hand, in the neuroses there is a notable variation in the intensity of the pain as described by the patient.

Dyspnea is not a common accompaniment of pain, though occasionally a paroxysmal dyspnea appears with the pain. In one reported case²³ the attacks could be averted by deep breathing.

In certain instances in which pain does not occur the patient may remain perfectly still during the attack and in every respect behave precisely like a patient experiencing the usual agonizing pain. Patients frequently experience in their seizures other symptoms in lieu of pain and such symptoms may be considered as equivalents of pain. According to Libman²⁴ these pain equivalents are more frequently noted in individuals who are hypersensitive to ordinary painful impressions. Not infrequently, in lieu of pain, dyspnea of an arresting type is experienced. This is sudden, paroxysmal, often nocturnal and accompanied by the classical sense of impending death, lasts during the attack and may disappear as suddenly as it appeared.

A similar clinical syndrome in which the dyspnea does not disappear may be due to a thrombotic closure of a coronary vessel.

I have seen several instances of coronary occlusion in which the predominating and initial feature was sudden dyspnea. Two seizures occurred by coincidence in a theater. In one a well known actor was forced by dyspnea to stop in the midst of his lines, in the second instance a woman of 50 years was seized with such sudden and urgent air hunger that she had to be carried from the theater. She had no pain at any time, but a terrifying dyspnea, yet she presented all of the usual signs of infarct, including a pericardial rub. Both of these cases showed unmistakable evidence of occlusion, neither had significant pain.

Profuse localized sweating may occur as an equivalent of pain. Such sweating should not be confused with that which commonly occurs with the shock of coronary thrombosis, nor with the less marked sweating of angina pectoris.

Palmer²⁵ reports a case of a physician of 61 years who, two weeks after an attack of precordial nocturnal pain, lasting one hour and requiring morphine, awoke to find the precordium, shoulder and left arm drenched with sweat, elsewhere no sweating. There was no pain, pressure or heaviness. He had had similar painful attacks two and six years previously. This case is reported as a case of angina pectoris.

Mackenzie notes local flushing and sweating with angina pectoris attacks. Vaquez notes fleeting vasomotor phenomena in angina pectoris. Osler²⁶ described one case in which profuse sweating preceded an attack of pain by one-half hour which, however, may have been an attack of coronary thrombosis with late pain. These changes represent reflexes from the heart or aorta to sweat glands, ciliary muscle or to end organs in the abdominal viscera.

A doctor of 67 years who, at the onset of his attacks had typical anginal seizures and later an occlusion, has during the past two years had attacks without pain initiated by marked salivation, nausea, and vomiting. If he stops at the onset of the attack, only the salivation occurs. After the attack he voids copiously. This has recurred frequently and over a long period and has not been associated with physical or electrocardiographic changes indicative of infarct. Save for the absence of pain and the symptoms described, the patient's sensations are those of his former anginal attacks.

Paroxysmal headache, vertigo, nausea and vomiting, and a sudden feeling of great weakness have all been described by reliable clinicians²⁷ as pain equivalents in angina. In some instances these appeared in the course of a classical angina as phenomena substituting the pain, in others they represented the presenting symptoms in a patient who was thought to be free from any cardiac complaints, yet died suddenly and showed at autopsy coronary or aortic disease without other cause for sudden death. It is probable that the vagus nerve plays a rôle in this confusing symptomatology. This nerve furnishes not only motor, but large sensory branches to both the gastrointestinal tract and the heart. In addition, there are numerous sympathetic pathways between these two systems. By either of these routes it is possible for pain or other symptoms to be registered as from a tissue in which it does not truly arise.

RELATIONSHIP BETWEEN THE SYMPTOMS OF CORONARY DISEASE AND CONGESTIVE HEART FAILURE

Angina and heart failure are antagonistic conditions. The failing heart is incapable of causing the true anginal seizure. With the control of failure

with digitalis, the muscle may recover sufficiently to cause a return of the painful attacks which existed prior to decompensation. In failure, local anoxemia exists, the muscle performs inefficiently. Certainly disturbed metabolism of the heart muscle is present, but nothing comparable to the seizure of angina pectoris occurs unless coronary thrombosis develops. The most satisfactory explanation for this so far advanced is the fatigue anoxemia theory previously mentioned.

When occlusion occurs in the course of heart failure, if not immediately fatal, the symptoms characteristic of thrombosis may not appear at all. To the existing failure there is only an increase in already existent symptoms, often without any acute pain.

THE ELECTROCARDIOGRAM IN CORONARY DISEASE

The changes in the standard lead electrocardiogram in coronary thrombosis are too well known to require more than passing comment. These changes in the R-S-T complex are initiated within a few hours of the onset, rarely returning to normal within six to twelve months, and there are permanent alterations in about 25 per cent of cases. As a rule, in addition to fusion of the R- and T-waves, there are distinct T-wave changes, generally some degree of inversion, but this is inconstant. Lead IV or some type of chest lead has offered some assistance both in diagnosis and prognosis, but with this technic normal variations introduce considerable confusion, perhaps more than in the case of the standard leads. Until cardiologists can agree as to a standard or standard chest leads, cardiographic diagnosis must rest upon the original standard leads. While the electrocardiogram is of great value in diagnosis in many instances, it must be admitted that exact correlation between the lesion and the electrocardiogram is impossible.

Because of the progressive changes which take place after an acute closure of one of the coronary vessels, the greatest amount of information will be derived from serial electrocardiograms, preferably taken daily. In this manner transitional changes will be shown, which would be missed in single records. This need for serial curves in cases of suspected acute occlusion is manifested by the fact that in rare instances tracings may remain normal or only slightly abnormal for several hours following occlusion, a point of importance in the differential diagnosis of coronary thrombosis and of acute surgical conditions in the abdomen. Hurxthal²⁸ warns against too great reliance upon the electrocardiogram in such instances. Furthermore, changes in the curves characteristic of infarct may be produced by myocardial ischemia brought on by a sudden myocardial insufficiency when the force is insufficient to drive the blood through narrowed or even normal coronary vessels, there is not acute closure of the vessel, but ischemia just as surely follows.

The serial changes described as characteristic of infarction take place in a fairly short space of time, ordinarily hours to days. Similar

changes developing more slowly are known to be associated with a myocardial fibrosis sequential to a chronic progressive coronary sclerosis, therefore, it is necessary to consider the time element in the interpretation of progressive changes in the R-S-T complex

There are a few records of electrocardiograms during a spontaneous attack of angina pectoris²⁹ and several during induced attacks, in all of these the T-wave becomes flat or inverted and the S-T interval depressed.⁴ In 75 per cent of 40 anginal patients similar changes followed effort, not necessarily associated with³⁰ pain. Experimentally induced anoxemia furnishes curves identical with the preceding, but these are transient, completely disappearing with adequate oxygenation.³¹ It is probable, therefore, that myocardial ischemia is the immediate cause of these changes observed during attacks of angina pectoris

In spite of all that has been stated regarding anoxemia as a cause of anginal pain and its association with coronary sclerosis, the fact remains that fully one-third of the patients with angina pectoris present entirely normal curves in the standard leads of the electrocardiogram. It seems probable that further observations with chest leads will show changes in this derivation, both in the patient with mild coronary sclerosis and in the one subject to anginal attacks. However, until this technic becomes standardized we must recognize that the electrocardiograph fails to detect about 33 per cent of the cases in this group

OTHER CONDITIONS IN WHICH PAROXYSMAL ATTACKS OF PRECORDIAL PAIN MAY OCCUR

In many normal individuals hypochondriac or precordial pain or ache may follow effort. Usually this is low in origin,—probably never higher than the arm or shoulder. It is often lancinating, knife-like and of sudden on- and off-set. Due to the popular knowledge of sudden death in painful heart disease, there may be an associated anxiety suggesting the *angor animi* of angina pectoris, but rarely the compressions noted in angina pectoris. Not infrequently there is precordial tenderness associated with pains in this region which are not due to heart disease

Esophageal or gastric distention may cause apical pain and may be relieved by belching or removing gas by the stomach tube

Rhythmic or arrhythmic paroxysmal tachycardia may give rise to precordial pains of varying intensity. These are not usually of the type and severity which would cause confusion with angina pectoris, moreover, the patient clearly recognizes the sudden disturbance in rhythm, and it is not as a rule until this has continued for some time that pain is significant. The associated drop in blood pressure may so reduce the coronary flow that anoxemia develops. Rarely does the picture of shock appear until the attack has continued over many hours. I have seen recurrent precordial pain and tenderness in a boy of 17 years whose paroxysmal auricular tachycardia

returned each time digitalis in large doses was withdrawn. White³² reports an exceptional case of bilateral anginoid pain severe enough to justify a consideration of alcohol injections, and four cases in which definite attacks of angina pectoris were brought on by paroxysmal auricular fibrillation or flutter.³³

Certain patients who are found to have sclerosed coronary arteries exhibit pain of less sharp though paroxysmal character, due to intermittent ischemia. Rest and vasodilators furnish relief. These pains may show some radiation, but in none of this group are the associated symptoms of angina pectoris present. This syndrome may represent an early manifestation of angina pectoris, yet many of these patients (perhaps one-third) will, with proper management, show nothing more for years.

Experimental studies³⁴ indicate that anoxemia plus work results in pain in the muscle involved, an observation which seems adequately to explain the effort pain observed by the patient with coronary sclerosis. Not all cases of coronary sclerosis complain of pain, about 20 per cent develop an ultimate myocardial failure without pain at any period, the balance (80 per cent) complain of pain or dyspnea at some time. The pain in this group is characteristically a sense of fullness or pressure, like a constricting belt rather than an acute pain. It is usually substernal or precordial, and in only about one in ten does it show any significant radiation, and then more often to the epigastrium, when, if accompanied by nausea and vomiting, the impression of an acute indigestion is strengthened. Dyspnea may be suffocating and not at all associated with exertion, in fact, the dyspnea of coronary sclerosis is most frequently nocturnal. There are instances of relief from mild exertion. This type of pain is to be differentiated from angina in that it is not dependent upon effort, worry or cold, is less paroxysmal, and there is no associated and characteristic posture, some degree of dyspnea rarely being absent.

An easily differentiated type of precordial pain is that associated with advanced myocardial disease. Here the pain is rarely of the severe arresting type, is precordial and without radiation. This pain, the associated dyspnea and peripheral signs of failure, often clear under digitalis therapy.

In advanced valvular disease, especially stenosis of the mitral and aortic valves, paroxysmal pain may occur. In the first instance it is thought that the coronary vessels are collapsed following sudden increase in intra-auricular pressure, in the second, sudden drops in an already reduced pulse pressure lead likewise to a decreased coronary flow.

Mention has been made of disturbed thyroid function. In both hyperthyroidism and in the hypothyroidism of myxedema rather typical anginal symptoms may occur. Approaching diabetic coma and the hypoglycemia of insulin shock may be accompanied by such a painful picture. Not infrequently in profound anemias painful attacks occur which strongly suggest angina pectoris. In this condition the myocardial demands exceed the available oxygen supply and a transient myocardial anoxemia ensues.

Rupture of the aortic valve or of an aneurysm of either the thoracic or abdominal aorta may present the clinical picture of coronary thrombosis. In one such instance³⁴ an electrocardiogram characteristic of infarct was obtained, which may have been due to a relative myocardial ischemia without infarction.

The upper abdomen presents surgical emergencies which often are only with great difficulty and loss of time differentiated from acute coronary occlusion. Because the electrocardiogram is at times a bit tardy in presenting its evidence, it behooves one to weigh all clinical evidence carefully before denying surgery. An exploratory operation in the presence of an infarcted heart is no greater error than an unoperated ruptured ulcer.

Not all of these abdominal conditions which may become confused with angina are potential surgical emergencies. The sigmoid colon may give rise to transient pains which appear to arise in the precordium and may even radiate to the shoulder and arm. The associated anxiety state induces palpitation and arrhythmia, thus completing a cardiac picture.

An occasional source of confusion is a pulmonary artery embolism. The immediate signs and symptoms may be identical with those of coronary occlusion. If the left lower lobe is infarcted there will be in a short time an accompanying pleuritis which may overlie the pericardial sac. Here the initial symptoms, the fever, leukocytosis and the apparent pericardial rub, all point to the heart as the primary seat of trouble. If this occurs in a patient with evidence of peripheral varicose veins or phlebitis or after operation, the likelihood of embolus is strengthened. Fortunately, the early management of such cases is so nearly identical that a diagnostic error is not very serious.

Spontaneous pneumothorax may for a time be confused with occlusion, the resulting enfeebled heart sounds, signs of shock, and thoracic pain being readily attributed to the heart. About 25 years ago, even before we were as "coronary conscious" as at the present period, I saw such a condition in a man in his late thirties in whom, there being no antecedent pulmonary history, the heart was under suspicion until roentgen-ray showed a small anterior pneumothorax not demonstrable by physical means.

Another pulmonary condition which, according to Hamman,³⁵ is likely to be confused with coronary thrombosis is spontaneous interstitial emphysema. The sudden tearing of mediastinal tissue may produce severe pain, although I have observed two instances which occurred in the course of induced pneumothorax, which were not accompanied by any appreciable pain, though sufficient to lead to a widespread emphysema of the cervical tissues. Hamman describes a peculiar "crunching sound" with each heart beat which might be mistaken for a pericardial rub.

Aside from the painful seizures of angina pectoris, the only heart condition which should be confused with coronary thrombosis is the occasional instance of pericarditis, often pneumococcal in origin, in which the pain

comes on as suddenly as in coronary thrombosis and is very severe and may radiate to the arms. This may shortly be followed by evidence of myocardial insufficiency. Here the complete clinical picture of coronary thrombosis, pain, dyspnea, circulatory failure, collapse and eventual congestive heart failure, combined with a pericardial rub, may tax diagnostic powers. Added to this picture we have electrocardiographic changes due to pericarditis which may suggest occlusion. A differential point is that in pericarditis the rub is louder, over a greater area and more constant, while in cardiac infarct the rub when present is faint, usually transient and limited in the area over which it is heard. A demonstrable pericardial effusion is rare in cardiac infarct.

The pain of sub-deltoid bursitis may simulate that of coronary disease, and in cardiac infarct persistent shoulder pain may direct attention away from the heart. Mild or severe, burning, aching or wrenching pain in the shoulder region was encountered in 10 per cent of 14 survivals from coronary thrombosis.³⁶

Disturbances of the spine and nerve roots presenting the radicular syndrome, when involving certain cervical and dorsal segments, may present a pain pattern very like that of true angina. These are commonly associated with postural defects and fatigue, and may be temporarily increased by anything which increases intra-spinal pressure, namely, coughing, straining, et cetera. Such phenomena as nausea, vomiting, and vasomotor changes, which are commonly associated with the pain of thoracic visceral disease, are not present in even the most extreme instances of root pain, and this pain is not relieved by nitrites.³⁷ A policy of "watchful waiting" in doubtful cases may relieve one of the embarrassment of changing the diagnosis of angina to one of herpes zoster, sciatica, lumbago or some other complication of spinal cord disease.

Diaphragmatic hernia has been confused with angina pectoris. In a recent report³⁸ a case of "diaphragmatic flutter" was described as simulating angina pectoris. The same patient subsequently came under my observation and will be the subject of an early report. This man entered the hospital with an admission diagnosis of angina pectoris, but was seen by me during an attack. That there was pain was evident, but here the patient was in constant motion and agitation and pounded his left precordium so violently it was thought that subsequent tenderness resulted therefrom.

This patient well illustrates the subject of false angina, the pseudo-angina of some writers, a term better discarded. As stated before the patient suffering from a true anginal seizure while in obvious distress is too concerned with the attack to wish or ask for sympathy, in fact, he is often remarkably quiet, while the subject of false angina presents exactly the opposite picture, his voluble description of his attack at once suggesting a neurotic background as a basis for his complaints.

The same type of patient complains of apical or precordial distress after

any psychic trauma grief, worry, surprise, even extreme pleasure Here the pain is rarely substernal or referred These patients both in military and civil life demand considerable attention They have been described under many names, probably neuro-circulatory asthenia or effort syndrome is the best

There is another type of precordial pain which has been frequently classed with the neuroses and certainly presents the general picture of a neurosis, but which is truly toxic in origin I refer to the dull ache, occasionally severe pain, noted by those who have become sensitized to tobacco, tea and coffee This pain is rarely reflected, lasts for hours, but is not incapacitating, at no time does the patient appear ill Complete withdrawal of the excitant is followed by complete relief, likewise, only slight exposure in those sensitized is sufficient to cause recurrence of the pain

DIFFERENTIAL DIAGNOSIS

Concerning the differentiation of those non-cardiac, but true disease entities with which coronary artery disease may be confused, enough has been said The anemias, hypoglycemias, valve and aortic ruptures, surgical abdomens, pulmonary conditions, and so forth, while a cause of temporary diagnostic embarrassment, are usually susceptible of differentiation after careful investigation, but after these are excluded there remain the larger numbers of either true instances of mild to severe cases of angina pectoris and coronary thrombosis, or a probably larger number of these cases of "false angina" Too great reliance cannot be placed upon the *angor animi* or sense of impending dissolution so strongly stressed by early writers This is in part dependent upon the psychic pattern of the individual, although there is a peculiar indescribable sensation associated with some anginal seizures which is not entirely dependent upon the severity of the pain As indicated before, probably the most conclusive evidence is the appearance of the patient during the attack In angina pectoris it is a rare experience for the physician to observe the attack, and the description of the lay observer is not too dependable

Standardized exercise tests which are both safe and yet sufficient to precipitate attacks of true angina pectoris have been introduced These tests offer an opportunity for careful observation³⁹ during an attack brought on in the office or hospital, and for observations as to results of therapy At least in those cases in which physical effort is the major factor, this method should prove a valuable means of differentiation from the false anginas

The hysterical patient can with ease and abandon present for anyone interested an excellent simulation of an anginal attack While it is true that organic heart disease may co-exist with a cardiac neurosis, this is not usually the case In general, it may be stated that evidence of organic heart disease, as enlargement, enfeebled heart sounds (in absence of a pulmonary or pleural cause for the same), persistent hypertension, or any electrocardio-

graphic evidence of coronary vessel or heart muscle disease, is acceptable confirmatory evidence of coronary disease, angina pectoris, or thrombosis when the clinical aspects suggest one of these conditions. The converse unfortunately is not quite true in the case of angina pectoris, for more than occasionally one will encounter a patient with the typical anginal syndrome in whom there is no demonstrable clinical, roentgen-ray or electrocardiographic evidence of heart change. Rarely these patients die without ever presenting any further evidence. In this group the final opinion is only arrived at after the elimination of all other possibilities. Sometimes only a sudden death establishes proof of organic disease.

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ANGINA PECTORIS AND PERNICIOUS ANEMIA (OLD TERMINOLOGY), A RÉSUMÉ OF THE LITERATURE, WITH A CASE REPORT

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HERRICK and Nuzum¹ in 1918, were the first to describe cases of pernicious anemia with symptoms of angina pectoris. They found four such in a group of 200 cases of primary anemias. Three of these patients died, one of anginal seizure. On none was a necropsy obtained. In 1927 Herrick² added two cases to his original group. He further stated that a very careful search of current literature during the previous nine years bore him out as to the relative infrequency of this syndrome.

Hunter,³ Evans,⁴ Sturgis,⁵ Levine,⁶ Conners,⁷ Elliott,⁸ Beach,⁹ Smith,¹⁰ Donald,¹¹ and Colvin¹² each told of but a single case, while others quoted from larger statistics. Reid¹³ in 1923 reviewed the postmortem records of cases of pernicious anemia at the Boston City Hospital from 1916 to 1921 and found 11 cases which presented cardiac aspects. Bullrich^{14, 15} of Buenos Aires has been widely quoted as having presented seven cases of this syndrome, but on a careful reading of his two papers, it would seem that only one of his cases might be pernicious anemia. Carey Coombs¹⁶ in 1926 wrote that eight of 36 patients with pernicious anemia, all of whom he had personally observed, suffered from cardiac pain. Wilkinson¹⁷ in a study of 370 cases of pernicious anemia found three cases with symptoms of angina or coronary thrombosis. Keefe and Resnik,¹⁸ Portei,¹⁹ Pickering and Wayne,²⁰ Hochrein and Matthes,²¹ Paschkis,²² Bloch,²³ Zimmerman,^{24, 25} Reichel²⁶ in large series of pernicious anemia cases found comparatively few with anginal symptoms. There have been no cases of this syndrome at Harper Hospital in the past nine years and, in the anemia clinic in 1935, 43 cases of pernicious anemia were diagnosed and treated.

Herrick¹ in his first paper assumed that blood of poor quality going through somewhat narrowed coronary arteries might favor on slight provocation the development of an anginal attack. On observing patients with severe anemia he was frequently impressed with the remarkable degree of circulatory efficiency that was maintained. From this and other papers quoted, the consensus of opinion might be stated in the following quotation of Levine,⁶ "Even with one-twelfth of the normal number of red blood cells, I do not believe that the anemia would initiate an attack of angina without some background of coronary disease." Many have reported improvement and often complete cessation of anginal attacks following transfusion, and, more recently, anti-anemia therapy. White²⁷ stated "although it is the anemia and not the heart trouble that has usually been responsible for death, congestive failure and angina pectoris have been seen in rare cases." Re-

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cently he told me he had seen a few cases with this syndrome and felt that the angina was due primarily to some coronary sclerosis or even spasm as described by Leary

But on the other hand Cabot²⁸ wrote of three cases of intense and typical angina associated with pernicious anemia and without coronary change. One showed a moderate sclerosis, the others none. To quote him, "Such cases certainly make us skeptical of any etiology wholly on organic and permanent changes either in the coronaries or in the aorta." Willius and Giffin²⁹ reviewed the records of 1560 cases of pernicious anemia and found but 43 (2.7 per cent) with symptoms of angina. Their conclusions were that the anginal syndrome in pernicious anemia is due to anoxemia of the myocardium and not to coronary or aortic sclerosis.

AGE AND SEX

White²⁷ stated that men presented anginal symptoms three times as often as women and that three-quarters of the cases of angina were past 50 years. Lewis³⁰ gave 45 years as the average age, Zimmerman in his series found that women had angina more frequently than men, and that the average age of patients with angina was 57.3 years, while for patients who presented the syndrome of angina pectoris and pernicious anemia the average age was 60.1 years. Lee and Minot³¹ stated that they had seen more men than women with pernicious anemia and that their ages ranged between 40 and 55 years. Schleicher³² quoted 53.7 years as the average age of patients in his group of pernicious anemia.

PHYSIOLOGY

In 1922 Fahr and Ronzone³³ studied a case of pernicious anemia with a hemoglobin of 12 per cent, 1,560,000 erythrocytes, and an oxygen carrying capacity of only 2.2 c.c. per 100 c.c. of blood (normal is 5.5 c.c.). The minute volume of the blood was increased proportionately. There was no dyspnea, no cyanosis, no increased pulse rate, and a normal basal metabolism or rate of oxygen consumption. A necropsy revealed a dilated heart with moderate increase in the thickness of the ventricular musculature. Their conclusions were that in severe anemias, the increased minute volume, due largely to lowered blood viscosity was the outstanding compensatory mechanism for loss of oxygen carrying power of the blood. The pathologic changes in the heart muscle in pernicious anemia might well be due to lack of oxygen as the coronary circulation was taxed to the upper limit and was comparable to that in strenuous work. It is well recognized that profound circulatory changes may occur in anemia, Liljestrand and Stenstrom,³⁴ and Richards and Strauss³⁵ have shown that the cardiac output is increased in anemia, Dautrebande³⁶ found a 300 per cent increase in cardiac output at a hemoglobin concentration of 20 per cent, with a return to normal value when the hemoglobin concentration rose above 50 per cent. Thus he found

over several months as long as the hemoglobin was above 50 per cent Kisch³⁷ thought it was probable that a deficiency of the capillarization of the myocardium was an important factor in the development of the attacks of cardiac pain. Rothschild and Kissin³⁸ showed that in eight of 11 patients who suffered from angina pectoris, pain could be induced by breathing air deficient in oxygen and ascribed the pain to the direct effect on the myocardium. Dietrich and Schwiegl³⁹ thought that during an attack of angina pectoris there existed an ischemia of the cardiac muscle and that not only the changes in the electrocardiogram but also the pains were a result of this ischemia.

Lewis⁴⁰ from his experiments upon human voluntary muscle inferred that myocardial anoxemia was not the direct cause of anginal pain. He felt that such pain must have a physico-chemical basis and must be attributable to a change in the conditions in the tissue spaces outside the muscle fiber. On the basis of this view it follows that the avoidance of pain in muscle depends upon adequate irrigation with blood, which removes the pain-producing substance, thereby preventing its accumulation in sufficient amount to cause pain.

Although the reaction of heart rate and blood pressure to exercise is usually altered in anemia and such alterations may contribute to the development of anginal pains, it may be assumed that the precipitating factor in the production of anginal pain in anemia is the lack of oxygen, which acts by producing a physico-chemical state that is the concomitant of pain. The anemic patient may be stopped by one of four events—breathlessness, giddiness, angina, or intermittent claudication. If the coronary arteries are diseased the relevant event will be angina, if they are not, then it will probably be breathlessness or giddiness. But in some patients, for a reason that is not yet at all clear, breathlessness and giddiness seem to be less easily induced and exercise may be carried on to the point of producing angina pectoris even in the absence of local disease of the vessels.

PATHOLOGY

The most constant finding has been fatty degeneration of the myocardium. This change in the heart muscle is found in a variety of conditions and seems not to be inconsistent with perfect health. The fat is not due to a degeneration or breaking down of the muscle fibers, but is brought by the blood stream and deposited in the heart, and evidence is lacking that the myocardium is impaired thereby. In Reid's¹⁸ cases enlargement of the heart of a degree that should be recognized clinically was not found, in six cases the actual weights of the hearts were between 240 and 340 grams, and in five between 300 and 400 grams. The hearts in this group of 11 necropsies showed the myocardium microscopically to be abnormal in only two cases. In these there were areas of necrosis of the fibers. In four instances the endocardium, especially on the papillary muscles, was mottled

and streaked with yellow, the so-called tigroid appearance. The epicardial fat was recorded as moderately increased in four cases and greatly so in two; otherwise these hearts were normal, save for moderate sclerosis of the coronary arteries in four, of the mitral valves in five and of the aortic cusps in two. Willius and Giffin²⁰ reported a necropsy on a woman of 55 with this syndrome. The heart was small and apparently normal except for fatty changes in the myocardium. Coombs¹⁶ had one postmortem only, it showed a diffuse atheroma of the aorta. The coronary arteries were not mentioned. At necropsy Elliott⁸ found in his case that the tigroid markings usually seen in cases of pernicious anemia were absent. By microscopic section there was no evidence of coronary or myocardial disease. Two of Reichel's²⁶ three patients came to necropsy. The heart of one had dilated chambers, normal aorta and valvular apparatus, and, microscopically, vacuolization of the muscle bundles. The second patient had arteriosclerosis of the aorta, fatty change of the left ventricle, and an area of myomalacia. The coronary arteries were not specifically mentioned in either instance but the finding of myomalacia in the second suggests the presence of coronary disease. Four cases in Zimmerman's^{24, 25} series of pernicious anemia came to autopsy—two with angina and two without. All four showed the same thing—complete calcification of the coronaries. There are at least five cases described (Cabot,²⁸ Willius and Giffin,²⁰ and Elliott⁸) in which no changes in the coronary vessels were found postmortem.

ELECTROCARDIOGRAMS

Pickering and Wayne²⁰ examined the electrocardiograms of 10 of their cases of severe anemia. In one with angina pectoris which persisted after cure of the anemia, there was a left ventricular preponderance. In two cases, the P-R interval was longer than normal when the patient was anemic and within normal limits after cure of the anemia. In the first case the P-R interval was 0.265 second when the hemoglobin content of the blood was 35 per cent and fell to 0.19 second when the hemoglobin content was 97 per cent. In the second case the corresponding figures were 0.205 second at a hemoglobin content of 38 per cent and 0.145 second at a hemoglobin content of 110 per cent. In the other cases no abnormality was noted during the anemic state. Curves taken immediately after the end of exercise in three anemic cases showed no changes in the shape of the R-T segment or any changes other than those directly attributable to exercise alone.

Reid¹³ found the QRS-T interval of normal duration and concluded the increased output of the heart was not accomplished by a lengthening of the ventricular systole. On examining 20 tracings he found nothing that might be considered of diagnostic value or as peculiar to pernicious anemia. Porter¹⁰ found in one case a slight left axis deviation and an isoelectric T-wave in Lead I. Reid,¹³ Willius and Giffin,²⁰ Hochrein and Matthes,²¹ Bloch,²³ and Smith⁴¹ felt that there was no typical electrocardiographic picture.

CASE REPORT

In May 1931, the patient, a male, 53 years of age, while at work suffered a severe, crushing, oppressive pain under the sternum. Previous to this he had experienced only an occasional mild attack. He was taken home and a physician was called who gave a small amount of digitalis, but no narcotic. The pain lasted about 24 hours, during which time the patient expectorated some pink sputum. Following this he remained in bed for two weeks and, after a few days' convalescence, returned to his work. For the next two months he was symptom free. Then he consulted another physician who treated him for diabetes although sugar was found in only one specimen. For one and a half years he had no severe attacks but everything he did was done with effort. His appetite was poor. During this period he was seen every two months by his physician.

In August 1933, the patient had a severe attack and another doctor was called. Following the immediate treatment he gave him hypodermic injections of iron and arsenic for anemia two to three times a week for eight months. From that time on he had frequent substernal pains. During February and March 1934 while working at night the patient had many severe attacks of pain radiating down both arms which never lasted more than 15 minutes. These attacks of pain came on at any time, after eating, or while sitting still, and were always accompanied by violent attacks of coughing. He also complained of frequency of urination. About this time nocturnal dyspnea began. In April 1934, his physician ordered an electrocardiogram which was reported as normal and hence he gave a favorable prognosis. Because of no improvement in his condition the patient sought another doctor and in August 1934 he had another electrocardiogram which showed left axis deviation and ventricular extrasystoles. For his pain he was never given nitroglycerine but always morphine sulphate by hypodermic injection which was invariably followed by nausea and vomiting. Still another physician saw him and suggested that he might have cancer.

The patient was first seen by the writer, following a severe attack of pain under the upper sternum September 15, 1934. A few additional items were added to his history. The pain even awakened him at night and frequently lasted for one and a half hours. It was very sharp, except occasionally when it diminished to a duller discomfort. Frequently it was located near the epigastrium and seemed to follow a rotary motion. Occasionally it spread out in oblong fashion and his arms pained terribly at the same time. Sometimes it was relieved by coffee.

Usually his bowels were regular. There had been some loss of weight, perhaps 20 pounds. Sometimes there was noted a slight edema of ankles and feet. He felt very weak, his appetite was poor, he ate no meat. He had been on digitalis and euphylline but had stopped taking them because of nausea.

He had never suffered with sore tongue, digestive disturbance, paresthesias, or anesthetics of fingers or toes.

The patient's past history was irrelevant except for a so-called attack of gall stones 11 years previous, with no recurrence. The patient denied venereal disease.

In the family history it was noted that his father had died at 64 "instantly, after working in field." One brother died of angina at 68. One sister, living, has angina at 69.

Physical Examination The patient appeared moderately well-developed, poorly nourished, and much older than his stated age. His height was five feet six inches. His hair was streaked with gray, the skin was rather sallow, flabby, and somewhat dehydrated, the eyes showed an arcus senilis, and the sclerae were slightly yellow, the tongue was not noticeably smooth, the papillae were of moderate size.

The heart was definitely enlarged both to left and right. There was an accentuation of the first sound, a gallop rhythm, a systolic and a rumbling diastolic

murmur at the apex, and also a very loud diastolic murmur at the aortic area and along the left border of the sternum. The pulmonic second sound equaled the aortic second. The pulse was 84. There was noticeable pulsation of the neck vessels. Blood pressure was 120 over 50 millimeters of mercury. The liver and spleen were not felt. The knee jerks were active and equal.

Laboratory Findings Urine examinations were essentially negative. The Kahn test was negative. Hemoglobin 53 per cent (Sahli), red blood cells 1,560,000 per cu mm, color index 1.7, mean diameter 8.3, white blood cells 4,500 per cu mm, stab polymorphonuclears 5 per cent, segmented polys 47 per cent, lymphocytes 41 per cent, eosinophiles 1 per cent, monocytes 5 per cent, basophiles 1 per cent. There were two 7 lobed polymorphonuclear neutrophils, one 3 lobed eosinophile, and one nucleated red blood cell seen, marked anisocytosis, poikilocytosis, many slightly oval forms, some achromia, some cells well-filled with hemoglobin.

A diagnosis was made of hyperchromic macrocytic anemia, angina pectoris, and aortic regurgitation and stenosis.

Treatment Because of marked dyspnea the patient was digitalized. He was also given ephylline grains $1\frac{1}{2}$ three times a day, frequent high caloric feedings, nitroglycerine grains $1/150$ as needed for pain, small amounts of whiskey and brandy, and two cubic centimeters of Parke Davis liver extract parenterally daily.

The patient had a bad cold twice, and because the increase of red blood cells seemed at times to be very slow, the liver extract was increased to four and for a short time to six cubic centimeters daily, as it is known that any factor, such as constipation, cold or infection, is enough to inhibit hematopoiesis. Once, following the injection of 6 cc, the patient experienced bulging of his ear drums and stated that there was palpitation of his heart. He felt weak and had to lie down as soon as he reached home. The symptoms lasted but a very short time.

The patient was always able to relieve his substernal pain with nitroglycerine and after one week, when the red blood count had reached 2,450,000 and the hemoglobin 71 per cent, he rarely had an anginal attack unless he exerted himself more than normally. As will be noted the red blood cells reached 5,000,000 in a little less than three months.

Following the intravenous liver he took ventriculin and kept his red blood count at a normal level. He filled out, his weight increased 10 pounds, his appetite was tremendous, and his general well-being was that of a man on the road to recovery. But his heart always showed a very loud aortic diastolic murmur and to the end the aortic second sound remained louder than the pulmonic second. The patient had an occasional attack of cardiac asthma.

Because he felt so well, he returned to his work, which was very light, shortly after the first of January 1935. On the third day following his return to work, he had an unusually severe anginal seizure while carrying a very heavy bottle of water. Instead of dropping the bottle he held it while the attack lasted, this prevented his getting any nitroglycerine. From then on he went slowly down hill. His cardiac asthmatic attacks became almost continuous. He had an idiosyncrasy for morphine and pantopon, manifested by marked nausea and vomiting, but was definitely relieved from his cardiac asthmatic attacks, without after-effects, by dilaudid given hypodermically and occasionally by sodium bromide and chloral hydrate by rectum.

As his cardiac asthma increased in frequency until it was almost continuous, his anginal attacks almost ceased. At the same time his appetite decreased and he was unable to continue with ventriculin. He began to show edema of lungs, abdomen, and feet which finally reached his knees. This was relieved by frequent intravenous injections of 2 cc of salyrgan. He became semi-comatose March 22, 1935, and two days later died in his sleep.

Autopsy Permission to examine the heart only was given. The findings were

as follows Weight 760 grams, left ventricular wall 27 millimeters, right ventricular wall 12 millimeters Grossly there were well marked fatty areas in the myocardium and a "tiger lily" appearance, especially of the papillary muscles There was functional insufficiency of all valves No signs of cardiac infarction either old or recent were found The aorta and the aortic valve showed marked sclerosis and calcification, and the cusps could not approximate The openings to the coronary arteries were enlarged, but on cross section through the arteries themselves they were found solidly calcified, barely admitting the tip of a common pin

SUMMARY

A case of angina pectoris and hyperchromic macrocytic anemia (with aortic stenosis and regurgitation, coronary sclerosis, cardiac asthma, and an idiosyncrasy for morphine) has been presented with a resumé of the literature bearing particularly on this symptom complex It apparently is not a common syndrome The anginal pains were relieved as usual with nitroglycerine but were less frequent when the blood picture approximated the normal, or at least, improved when a higher blood count was obtained The theory has been propounded that anoxemia is a factor initiating angina, and it is conceivable that, in pernicious anemia, blood of poor quality might readily aid in the development, on slight provocation, of an anginal spell Because the age period of both of these diseases is approximately the same it may be a natural occurrence that they are found together in the same patient It was felt by one investigator that patients with anemia do not very often develop angina because of their general easy fatigue which causes them to stop short of the danger point But as most patients with pernicious anemia do not have angina, the anemia per se cannot be a primary cause

Again the pathologic changes in the heart muscle in pernicious anemia have been thought to be due to lack of oxygen from the fact that the coronary circulation is taxed to the upper limit, comparable to the effects of strenuous work In general the consensus of opinion has been that there were no diagnostic abnormalities in the electrocardiograms and what changes were noted could be traced to a coincident atherosclerosis

CONCLUSIONS

The writer presents a case of angina pectoris with pernicious anemia and reviews the slightly over one hundred similar cases in the literature As so few cases of this syndrome have failed to show sclerosis of the coronary arteries, one may safely assume that most anginal pains in this symptom-complex result from anoxemia of the myocardium due to sclerosed coronary arteries But when in addition the blood is deficient in adequate oxygen carrying power, the functional capacity of the myocardium is still further diminished and angina occurs more readily Hence the incidence of cardiac pain in atherosclerosis with pernicious anemia is higher than in atherosclerosis alone

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BODILY BUILD AND HEREDITY IN CORONARY THROMBOSIS

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THE importance of habitus in its association with certain pathologic states has been the subject of considerable discussion in recent years. The coexistence of obesity and hypertension has often been emphasized. It has been our clinical impression that many individuals who have coronary thrombosis are overweight, but no adequate statistics are available regarding this question. The tendency for abnormal degrees of arteriosclerosis and their premature manifestation to occur with unusual regularity in certain families, and the proclivity of angina pectoris to be a familial disease have been recognized for many years.

To investigate the importance of bodily build and heredity in coronary thrombosis, 300 cases observed in the past few years at The Mayo Clinic have been reviewed. The diagnosis of coronary thrombosis was confirmed in these cases by postmortem findings, characteristic changes in the electrocardiogram, or a typical history of this condition at some time prior to our examination plus residual electrocardiographic changes. This group of individuals consisted of 272 men and 28 women who were between 40 and 80 years of age, 118, or 39 per cent of these patients, were between the ages of 50 and 59 years. In each case the following data were obtained: age, height, average weight prior to the patient's admission to the clinic, weight at the time of examination, detailed characteristics of bodily build whenever stated, and family history, including, whenever possible, the age and cause of death of parents and siblings. The presence or absence of cardiovascular renal disease in the family was noted.

Having obtained the present weight of each individual, this was compared with the average weight for the age and height, as given by the insurance standards. The weight of each individual has been expressed as a percentage difference from the standard weight according to sex, age and height. Figure 1 shows the distribution of weights expressed in these terms for the entire group studied, using the observed weight of the individual at the time of his examination at the Clinic. The mean deviation was +1.8 per cent. The weight varied from -42.5 per cent of standard to +47.5 per cent. The number of patients who were overweight slightly exceeded those who were underweight, 51 (17 per cent) were more than 15 per cent overweight, while 39 (13 per cent) were more than 15 per cent underweight. The weight of 13 patients exceeded the average weight by more than 30 per cent, while the weight of only one was more than 30 per cent less than the average.

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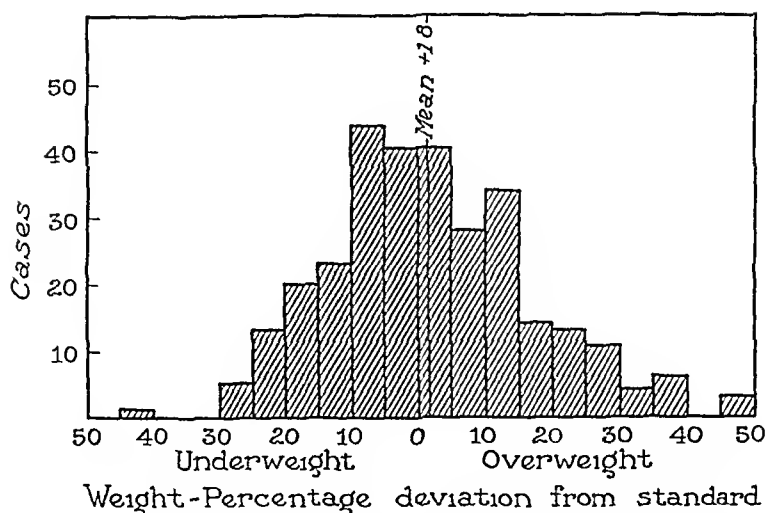


FIG 1 Distribution of weights of patients at time of examination at the Clinic, expressed in terms of deviation from standard weight according to sex, age and height

weight As previously stated, the weights used in plotting the graph in figure 1 were those determined at the time of examination at the Clinic. Many patients were very ill and had lost weight. It seemed appropriate to use the average weight of the patient prior to his illness instead of the weight as determined at the time of examination, and to compare the former with the standard weight. The results of this study are shown in figure 2. The

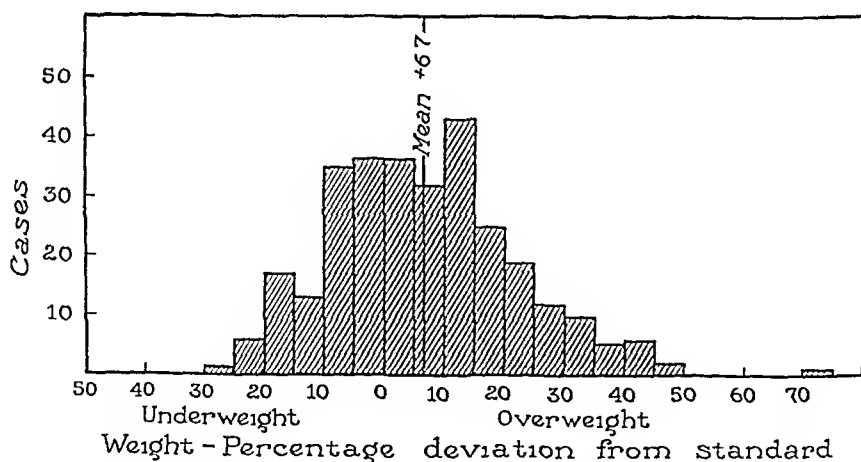


FIG 2 Distribution of weights of patients before illness, expressed in terms of deviation from standard weight according to sex, age and height

mean deviation from the average was in this instance $+6.7$ per cent. Only seven individuals gave a history of an average weight 20 per cent or more below the standard, while 55 individuals had an average weight of more than 20 per cent above the average. Thirty-seven individuals (12 per cent) were more than 10 per cent underweight while 123 individuals (41 per cent) were more than 10 per cent overweight, as determined by the standards used.

Figure 3 gives a more detailed analysis of the problem, the total group of women and the men in each age group were studied separately, except the five patients who were between 30 and 39 years of age, who were too

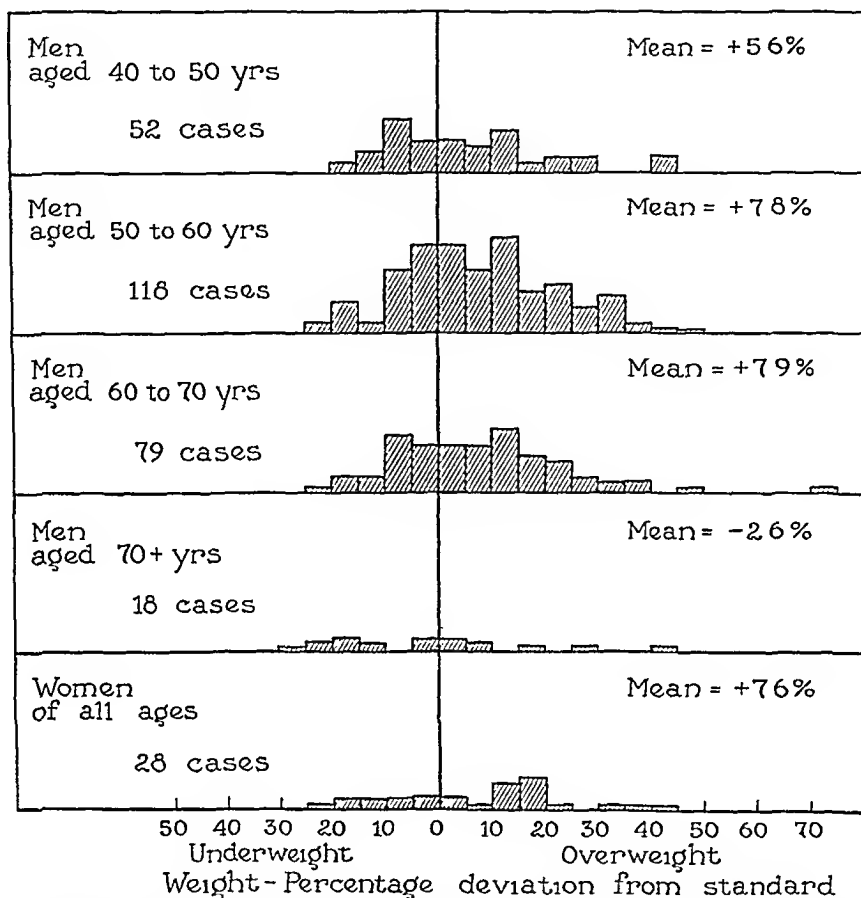


FIG 3 Distribution of weights of patients before illness, expressed in terms of deviation from standard weight for men and women separately and for specific ages for the men

few to be significant. The weight used was that which the individual described as his normal average weight prior to the onset of the presenting illness. The tendency to overweight is evident among patients of all ages except among the men who were more than 70 years of age. The findings obtained in this last group are probably partly the result of inadequate standards for this age. The men who were between 50 and 70 years of age and all of the women showed a mean deviation of more than +7.5 per cent from the average.

Details of habitus aside from a tendency to obesity, were meager. A number of individuals were described as plethoric, some were of the short stocky type and had thick necks, others were of large powerful build. A ruddy complexion or flushed face was often noted as was the fact that the individuals were often nervous and high-strung. In contrast to this a num-

ber of persons were obviously very ill, pale, sallow, or cyanotic, and revealed evidence of recent loss of weight. Apparently all types of bodily build were represented and the data were inadequate to determine statistically the predominance of any one type.

There was a family history of cardiovascular renal disease in 165 (55 per cent) of the 300 cases. Fifty-seven (35 per cent) of the patients said that two or more members of their immediate family (parents or siblings) had some type of cardiovascular disease. Eighteen patients said that both parents had died of heart disease or cerebral hemorrhage. The cause of death of one of the parents, or the cause of the death of siblings, was given as cerebral hemorrhage in 52, coronary thrombosis in 14, heart disease (type not stated) in 52, hypertension in five, dropsy in nine, nephritis in 23, and uremia in three cases, respectively. It seemed of interest to determine whether individuals who gave family histories of cardiovascular disease died at an earlier age than did their parents. Such data were available in 88 cases. In 70 cases, only one parent had died of this type of disease. It was discovered that 30 patients died at a younger age and 12 at a more advanced age than had the affected parent, while 28 were still living but had not yet attained the age at which the parent had died. In the 18 cases in which both parents had succumbed to cardiovascular disease, three patients died at a younger age than had either parent, seven died at a younger age than had one parent, six, who are still living, have not attained the age reached by the parents, and in two cases the age at which death of the parents occurred was unknown.

In the series of 165 cases in which there was a history of cardiovascular renal disease among other members of the family, 83 of the patients have died. The average age of the patients at the time of death was 59.2 years. Of the 135 patients who did not give any history of cardiovascular disease in the family, 50 have died, their average age at the time of death was 60.1 years. No conclusive information is gleaned from these figures as in both groups of cases the age of the patients at the time of death was apparently the same, although fewer deaths occurred in the group in which there was no family history of cardiovascular renal disease. The evidence presented suggests that the presence of cardiovascular disease in the family diminishes the chances of longevity. The high familial incidence of cardiovascular renal disease in this series of cases supports the view that there is an hereditary tendency for these pathologic conditions to develop.

In this group of 300 cases, there were 83 patients (28 per cent) who had hypertension. It was thought that the habitus in this group might differ from that of the group in which the patients did not have high blood pressure. Table 1 shows that in this series the weight of 59 per cent of the patients who had hypertension was at least 5 per cent more than the average weight for height and age according to the standards used, while only 48.85

per cent of those who did not have hypertension were more than 5 per cent overweight. Similarly, the group of patients who had hypertension included only 16 per cent of patients who were more than 5 per cent underweight, while the group of patients who did not have hypertension included 27 per cent of patients who were more than 5 per cent underweight. It is thus evident that the patients who had hypertension were inclined to be more obese than were those who had a normal blood pressure.

TABLE I

Relation of Weight of Patient to Family History and Value for the Blood Pressure

	Pa- tients	Percentage of patients who were more than 5 per cent under- weight	Percentage of patients whose weight was normal (+5 pounds to -5 pounds)	Percentage of patients who were more than 5 per cent over- weight
Family history of cardiovascular disease	165	23.03	24.84	52.13
No family history of cardiovascular disease	135	25.19	23.70	51.11
Hypertension present	83	15.66	25.30	59.04
Normal value for blood pressure	217	27.19	23.96	48.85

Table 1 also shows the percentage of individuals who were overweight or underweight and who did or did not give a family history of cardiovascular disease. Slightly more than 50 per cent of the patients in both groups were overweight by 5 per cent or more, as compared to the standards.

COMMENT

While the habitus of the patient does not appear to be of outstanding importance in the predisposition to coronary thrombosis, the occurrence of overweight in more than half of the cases is not without significance. This observation, moreover, is another indictment against obesity in general.

The data in this study do not permit the determination of conclusive facts regarding the hereditary tendencies to coronary disease, although the more than casual repetition of cardiovascular renal diseases in certain families is of interest and undoubtedly is of importance. The fact that it is virtually impossible to obtain reliable data regarding the causes of death, even among the patient's grandparents, to say nothing of preceding ancestors, makes the establishment of a hereditary continuity almost impossible, except in rare instances.

Nevertheless, clinical contacts with many patients over long periods of time create an impression that hereditary influences play a much more important rôle in coronary disease than is generally admitted.

SUMMARY

A study of the habitus of 300 individuals who had coronary thrombosis revealed a mean deviation of ± 6.7 per cent from the average weight for height and age. The individuals who had hypertension tended to be more overweight than did those who had a normal blood pressure. There was a family history of cardiovascular renal disease in 165 of the 300 cases. Familial predisposition to cardiovascular disease showed no correlation with the degree of obesity.

THE EFFECTIVENESS OF TRICHLORETHYLENE IN PREVENTING ATTACKS OF ANGINA PECTORIS¹

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TRICHLORETHYLENE has been used for some time in the treatment of trigeminal neuralgia. Its therapeutic activity in regard to this condition has been discussed by Glaser,^{1,2} and an extensive bibliography of its use for this purpose is given in his papers. It has also been used as an anodyne in dental procedures and for dental pain^{3,4} and with some success as an anesthetic for operations upon the face⁵. In a conversation with Dr. David Bryce in which the discussion turned upon angina pectoris, it was suggested by him that trichlorethylene might prove of use in preventing such attacks. The following investigations were then undertaken:

CERTAIN PHARMACOLOGICAL ACTIONS OF TRICHLORETHYLENE

After exhibition of this preparation had apparently benefited certain patients with angina pectoris, Dr. John C. Krantz, Jr., of the Department of Pharmacology of the University of Maryland, kindly undertook the study of certain questions in regard to the pharmacological action of this drug^{6,7,8}. His observations indicate that:

- 1 Trichlorethylene causes a constriction of the perfused vessels of the frog
- 2 It does not influence the oxygen consumption of rats
- 3 It has an irregular effect upon the coronary flow of the dog, at times increasing and at times diminishing this flow
- 4 It decreases the blood pressure and slows the heart rate in dogs
- 5 When applied directly to the sciatic nerve it fails to block the blood pressure and respiratory responses to faradization

He concludes that the drug probably causes hypalgesia by depressing the basal ganglia and perhaps produces a relaxation of the vessels of the splanchnic area while causing a peripheral vasoconstriction.

Pharmacological Actions of Trichlorethylene on Human Subjects In 27 patients with cardiovascular disease of some type, under treatment with this drug, there were 13 with systolic blood pressures of over 150 mm of mercury and diastolic levels of over 100. In this group of hypertensive patients, taking trichlorethylene by inhalation in 1 c.c. doses thrice daily, the systolic pressure fell from 20 to 30 mm. in four, and 40 or more mm. in two. The shortest period in which such a drop is known to have occurred

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The author is indebted to the Calco Chemical Company, Bound Brook, New Jersey, for supplying much of the trichlorethylene used in carrying out this investigation.

is one week, the longest six weeks. One patient showed a rise of 10 mm. The systolic pressure fell 20 mm in one patient not classified as hypertensive. Three normal individuals with normal blood pressures inhaled 1 c c thrice daily for three weeks. In two of these there was no significant change in the blood pressure. One consistently had an average fall of 20 mm in systolic and diastolic pressure, beginning during the inhalation and lasting for about 20 minutes. There was no permanent lowering of the pressure in this individual. Thus in 31 individuals subjected to the inhalation of 1 c c of trichlorethylene three times daily, there was an immediate and transient fall in blood pressure in only one, and in seven a significant fall occurring a week or longer after the inhalations were begun. It is probably of significance that six of these seven individuals suffered from hypertension, and that six of thirteen hypertensives presented such a reaction.

The following experiment indicates that such decreases in blood pressure are not associated with any marked impairment in the conductivity of reflex pathways.

W. M., aged 48 (case 24), known hypertensive for at least three years. Blood pressure at beginning of treatment, 190/130, two weeks later, 175/105, six weeks after initiation of treatment, 130/85.

Blood Pressure before test 135/85	Left hand immersed in ice water Blood Pressure in		
	30 seconds	1 min	2 min
	170/100	190/110	210/140

Skin temperatures have been determined by a thermopile before, immediately after, and after continued inhalation of trichlorethylene in three normal individuals. In two there has been no change in temperature and in one there has been a slight drop. This suggests that in the dosage used there occurs neither a marked peripheral vasodilator nor vasoconstrictor response to trichlorethylene in man.

There is not sufficient evidence at this time upon which to base an explanation of a reduction in blood pressure following the continued use of trichlorethylene. It is perhaps due to the sedative action of the drug.

The pulse rate has not been significantly altered in most individuals. A few have shown a transient rise of as much as 20 beats per minute. This is contrary to the results obtained by Krantz and his co-workers on dogs and is probably to be attributed to psychic reactions.

TOXICOLOGY

Joachimoglu⁹ considered the drug harmless. Krantz and his co-workers⁸ conclude that repeated anesthetizing of rats did not markedly influence their growth curves or subsequently lead to important pathological changes in their viscera. Eichert¹⁰ reports two cases of toxic psychoses following therapeutic use of trichlorethylene and quotes from Zulkis one of addiction to the drug with toxic effects. In all three cases gross overdosage had been

voluntarily taken by the patients. All recovered without demonstrable ill after-effects. Taylor¹¹ reports that following daily six hour inhalation exposures to trichlorethylene, rats survived six months when concentrations of 0.2 per cent or lower were used. Pathological examination at the end of the experimental period revealed no signs of degeneration in any organ. A concentration of 0.3 per cent proved too high, only two of six rats surviving six months.

No evidence of toxicity has occurred in any of the 28 cases of this series. One patient has been taking trichlorethylene from time to time for three years, and during the first year used it almost daily.

Alice Hamilton¹² discusses 284 cases of industrial poisoning supposedly due to trichlorethylene. In this group there were 26 deaths. While there is no decisive evidence on this point, it seems likely that such cases of industrial poisoning are due to substances other than pure trichlorethylene. Trichlorethylene on contact with air and light may form decomposition products among which phosgene has been identified.

METHOD OF TREATMENT

While some observations have been made upon the usefulness of this drug in relieving immediate attacks of angina pectoris and the pain of coronary thrombosis, the primary purpose has been to discover if anginal seizures would be prevented or diminished in frequency and severity by this drug.

Twenty-seven patients have been treated as follows: from two to four, usually three, inhalations of trichlorethylene have been given daily. Sealed frangible glass ampoules of one cubic centimeter are crushed in a handkerchief. The first inhalation has always been taken in the presence of a physician so that the immediate effect might be noted, and the patient reassured, if alarmed. Thereafter, patients are advised to take the drug either while reclining or sitting in an easy chair, for marked lightheadedness often occurs, and occasionally there is a brief loss of consciousness. The treatment is continued as above for three weeks. If no therapeutic effect has been achieved in this time, the use of trichlorethylene has been discontinued, and the method considered ineffective. Should the treatment prove effective, the number of inhalations is reduced in each individual to the minimum consistent with an adequate relief of symptoms.

THE EFFECTS PRODUCED BY THE INHALATION OF ONE C C OF TRICHLORETHYLENE THRICE DAILY, OTHER THAN UPON CARDIAC PAIN

When inhaled this drug is irritating to the mucous membranes of the respiratory tract and a sensation of burning commonly occurs in the nose, and the patient usually coughs, but not violently. Within a few seconds after the inhalation is started the patient complains of lightheadedness and

in about one-half this effect is marked. Such lightheadedness lasts only a few moments and leaves the patient mentally clear. Three patients of 27 lost consciousness for periods lasting from two to five minutes. Headaches subsequent to its use have not been noted. Five patients described a feeling of marked well-being, amounting to a mild euphoria. When the patient has been nervous and irritable and sleep has been restless, well-marked sedation, loss of irritability and quiet sleep have usually followed the exhibition of this drug. This, however, has not been accompanied by any dulling of the mentality of sufficient degree to be noticed by the patients or manifested by any loss of ability to perform their usual work. One patient became so alarmed at temporary loss of consciousness that this mode of therapy had to be discontinued.

EFFECT OF TRICHLORETHYLENE UPON THE PAIN ACCOMPANYING CORONARY THROMBOSIS

Six patients have been given trichlorethylene during immediate attacks of pain due to coronary thrombosis. Cases 1, 2 and 3 received the drug within 12 hours of the onset of such pain, and case 4 had been started the preceding day in the hope of preventing paroxysms of hypertension associated with anginal pain. In this last case thrombosis occurred after three inhalations. The patient lived for three days and trichlorethylene had no appreciable effect upon the pain. Cases 1 and 2 received immediate relief from pain. In case 1 the intervals between recurrence of pain were very irregular, and if additional trichlorethylene were inhaled at the beginning of the pain it was aborted within a few minutes. Case 2 lost consciousness for about five minutes after each inhalation, and freedom from pain was obtained for about one hour. Morphine proved more satisfactory for controlling pain in this patient who died on the seventh day of her illness. Case 3 received no relief with morphine in $\frac{1}{2}$ grain doses given twice before admission to the hospital. A single inhalation of trichlorethylene gave marked relief in a few minutes and the inhalation was immediately repeated, complete relief from pain being then obtained. Freedom from pain lasted from one-half to three-quarters of an hour, and it did not again become intense for about three hours. Inhalations were ordered for this patient at three hourly intervals and he was permitted to receive additional inhalations on request. After 72 hours only occasional inhalations were taken.

Cases 5 and 6 were seen five and seven days respectively after coronary thrombosis had occurred. As noted in the case histories, striking relief followed the exhibition of trichlorethylene to both of these patients. However, it is well known that the pain and distress of coronary thrombosis tend gradually to become ameliorated at varying times after their onset. One could not say in case 5 that this had not happened in the natural course of events. Case 6 offers more positive evidence of the rôle played by trichlorethylene in as much as morphine had previously failed to give relief up to

the moment the inhalations were started. In less than 12 hours after the initial inhalation this patient had his first restful night and sleep.

Thus in three of four cases seen within 12 hours of the onset of coronary thrombosis trichlorethylene afforded relief from pain, proving more useful than morphia in one case and less so in one case. In case 1 morphia was not used. In one case trichlorethylene was ineffective. In two more cases relief of pain followed the exhibition of this drug but because of the length of time elapsing from the occurrence of the thrombosis to the initiation of inhalation treatment, disappearance of the pain cannot with certainty be attributed to this treatment. It is possible that trichlorethylene was more effective than morphia in one of these cases. When successfully used, it had the advantage over morphia of not causing constipation.

Case 1 White male, aged 54. Hypertensive arteriosclerotic cardiovascular disease. Angina pectoris followed in six months by coronary thrombosis. Continued frequent recurrence of pain, severe, while in bed. Blood pressure very variable, before attack averaged 200 millimeters of mercury systolic and 120 diastolic, after attack fell to 140 systolic and 100 diastolic then rose to 180 systolic and 120 diastolic with paroxysmal elevations as high as 260 systolic and 160 diastolic. Slight relief with theobromine. Pain often aborted by single inhalation of trichlorethylene, and inhalations given three times a day prevented pain. The blood pressure became stabilized at about 175 systolic and 110 diastolic. The patient has been under observation two years, during which time there have been two apoplectic seizures. Cardiac pain recurs periodically and is relieved and prevented by trichlorethylene. Electrocardiogram just before attack of thrombosis. Leads I and II show the coronary type curve, a record 16 months later shows no essential difference. This patient is a very high strung, irritable individual.

Case 2 White female, aged 49. Coronary thrombosis. Blood pressure, 90 systolic and 70 diastolic. Died on seventh day. Trichlorethylene gave temporary relief lasting for about one hour after each inhalation. This patient was unconscious for about five minutes after each inhalation. Morphia proved more satisfactory in this case.

Case 3 White male, aged 48. Acute coronary thrombosis preceded by anginal pain on exertion for four days. Leads I and chest lead type of acute coronary curve. Blood pressure on admission, 150 systolic and 110 diastolic, dropping to 80 systolic and 60 diastolic. Pain not relieved by morphia. Relieved by trichlorethylene completely for one-half hour after inhalation and pain ameliorated up to two or three hours.

Case 4 White male, aged 50. Arteriosclerotic cardiovascular disease. Paroxysmal hypertension with anginal pain. Coronary thrombosis—died third day after onset. Blood pressure 120 systolic and 95 diastolic, going to 180 systolic and 120 diastolic in attacks. Electrocardiogram before attack. Normal mechanism. Trichlorethylene started day before thrombosis and continued to death. No relief.

Case 5 White male, aged 52. Arteriosclerotic cardiovascular disease. Coronary thrombosis with pain persisting in attacks for one week while in bed. Blood pressure 110 systolic and 80 diastolic. Electrocardiogram none. Complete relief in 24 hours.

Case 6 White male, aged 71. Arteriosclerotic cardiovascular disease. Coronary thrombosis with persistent pain, nausea and vomiting, complete incapacity five days after attack. Blood pressure, 120 systolic and 90 diastolic (stated to have previously averaged 170 systolic and 100 diastolic). Complete relief of pain within

12 hours after exhibition of trichlorethylene, restful sleep Morphua in 1/8 grain doses had previously failed to give relief Trichlorethylene continued one week, no recurrence of pain after drug stopped

TRICHLORETHYLENE USED TO PREVENT ATTACKS OF ANGINA PECTORIS

Of the remaining 21 patients, 18 had either arteriosclerosis or arteriosclerosis and hypertension combined, there was one case of syphilitic aortitis, one case of chronic nephritis, and one case in which there was a history of hypertension not found at time of examination Of these patients nine gave a history of having had an attack of coronary thrombosis not more than two years previously The electrocardiogram was normal in one, of the coronary type in 10, presented definite deviations from normal in nine and was not recorded in one All of the above patients presented angina pectoris as a symptom of their disease Trichlorethylene was inhaled by these patients as a rule three times a day In these 21 patients anginal seizures were prevented completely by the inhalations in eight, they were definitely diminished in frequency and severity in eight and moderately diminished in one This last patient had syphilitic aortic insufficiency and was receiving antiluetic treatment This of course may account for the improvement that was observed Four patients received no benefit from the inhalations In seven patients it was noted that the pain recurred as severely as formerly whenever the inhalations were discontinued, the period of time elapsing before its recurrence varying from 24 hours to several weeks The period of time from the initiation of treatment to the cessation of symptoms varied considerably, no attacks occurring in some instances after the first inhalation, and in others the improvement being gradual—case 25 did not achieve his maximum improvement until six weeks after beginning the inhalations In one patient* this treatment gradually lost its effect as a preventative in two months, but still could be effectively used to relieve immediate severe attacks of angina pectoris

The exercise tolerance of these patients has only been directly tested in case 26 In this case it will be noted that there was a definite increase in the amount of exercise performed without pain The pain, however, was just as severe when it was finally induced All patients receiving benefit from the treatment could do more of ordinary activities than was possible before it was commenced, and where such statements are definite, they are noted in the case histories

I have no data for an adequate comparison of the effectiveness of trichlorethylene with that of other drugs used for the relief of angina pectoris The above studies have been directed toward determining its effectiveness in preventing such attacks However, it has been noted to be effective for

* Since offering these observations for publication, case 23 has reported that prevention of attacks no longer results from inhalation of trichlorethylene and that he has had to retire from business because of their frequent occurrence when under mental strain Therefore there are two patients who have reported that the original beneficial effect of trichlorethylene inhalations did not last

the former purpose in several cases in which other drugs have been used. Thus in case 20 amyl nitrite had at first afforded relief from pain, but later failed to do so, inhalations of trichlorethylene were then found effective.

Five patients other than those with coronary thrombosis obtained immediate relief from anginal seizures, three specifically note that no relief was obtained. However, it is my present impression that there is little likelihood of this drug proving as effective for the relief of the anginal attack as are other already accepted methods of treatment.

There is no evidence that this drug in any way effects a cure, symptoms usually return when its use is discontinued.

CASES OF ANGINA PECTORIS

Case 7 White male, aged 37. Neurotic personality. Anginal type of pain, tight, retrosternal, radiating to left arm, occurring on unusual exertion or after large meals. Blood pressure, 150 systolic and 105 diastolic. Electrocardiogram slurring of QRS, T_1 inversion, large Q_1 . Pain prevented by theobromine which also caused vertigo and nausea. Trichlorethylene prevented attacks, none occurring after third day of taking drug. The pain recurred whenever the drug was discontinued. Blood pressure after trichlorethylene 130 systolic and 90 diastolic. Under observation one year. Died of pneumonia.

Case 8 White male, aged 47. Hypertensive cardiovascular disease. Coronary thrombosis one month previously. Continued severe attacks of anginal type of pain while in bed. Blood pressure, 170 systolic and 120 diastolic. Electrocardiogram Leads I and II type coronary curve. Complete incapacity. No relief from theobromine. Complete prevention of pain by trichlorethylene, the pain recurring when drug discontinued. Patient under observation three years and in the last 12 months has resumed his occupation, which requires much walking. Blood pressure after taking trichlorethylene, 140 systolic and 100 diastolic, and has remained at about this level. At the present time the patient has an occasional sensation of oppression behind the sternum and a single inhalation of trichlorethylene will promptly relieve this.

Case 9 White male, aged 60. Hypertensive arteriosclerotic cardiovascular disease. Two weeks previously there had been an attack diagnosed as acute coronary thrombosis. Continued attacks of severe precordial pain at times radiated to left arm, occurring while in bed. Blood pressure before attack, 190 systolic, immediately after, 130, for week preceding examination by me, 170, at time of examination, 200 systolic and 100 diastolic. Electrocardiogram none. Trichlorethylene completely prevented the pain, pain returned when drug was discontinued. This patient later took inhalations for the immediate relief of anginal attacks with success. Blood pressure from 185 systolic and 100 diastolic to 200 systolic and 110 diastolic. Patient living two years later, occasional pain, no regular medication.

Case 10 White male, aged 61. Hypertensive arteriosclerotic cardiovascular disease of two years' known duration. Angina pectoris of one year's duration. Eight months ago diagnosed coronary thrombosis. At time of examination doing office work several hours daily, very slight exertion caused constricting pain behind sternum radiating to both arms. Blood pressure, 260 systolic and 130 diastolic. Electrocardiogram Left axis deviation, T_1 and T_2 inversion. During the first two weeks of taking trichlorethylene there occurred only one attack of mild pain. Patient was walking eight blocks without difficulty. Blood pressure, 200 systolic and 110 diastolic. Two months later at full work, but occasional heavy sensation over precordium. Trichlorethylene discontinued. At present patient takes occasional

courses of theocalcin. Trichlorethylene in single inhalations failed to influence immediate seizures. There is now a severe arteriosclerotic retinitis with visual impairment.

Case 11 White male, aged 64. Diabetes mellitus, arteriosclerotic cardiovascular disease, angina pectoris. Blood pressure, 160 systolic and 110 diastolic. Electrocardiogram T_1 and T_2 inversion, arched ST segments. Pain occurs on walking a little rapidly, or on going up moderate hills, at times after meals. The blood pressure remained about the same after taking trichlorethylene. There was greatly increased but not complete freedom from pain while taking this drug, and the pain would recur several days after the drug was discontinued. This patient was followed four months.

Case 12 White male, aged 53. Diabetes mellitus, arteriosclerotic cardiovascular disease. Anginal pain occurring if patient walked four blocks. Blood pressure, 140 systolic and 100 diastolic and remained at this figure after trichlorethylene was used. There was complete prevention of pain. This patient was treated with trichlorethylene for only one month because of expense of treatment. Pain recurred after trichlorethylene was discontinued. Electrocardiogram normal.

Case 13 White male, aged 56. Diabetes mellitus, arteriosclerotic cardiovascular disease. Anginal pain produced by moderate exertion. Blood pressure, 150 systolic and 100 diastolic and not affected by trichlorethylene, which also did not affect the pain during three weeks treatment. Electrocardiogram left axis deviation.

Case 14 White male, aged 43. Hypertensive cardiovascular disease, neurotic type personality. Anginal type of pain, moderate exertion causing pain. Electrocardiogram left axis deviation, slurring of QRS waves. Blood pressure, 160 systolic and 120 diastolic. Blood pressure after trichlorethylene, 135 systolic and 95 diastolic. Theobromine derivatives gave this patient no relief. There was complete absence of pain while taking trichlorethylene, and the pain recurred when the drug was discontinued and the blood pressure returned to 150 systolic and 110 diastolic.

Case 15 White male, aged 38. Coronary thrombosis two years previously. Blood pressure 120 systolic and 80 diastolic. Electrocardiogram at time of occlusion acute coronary curve, Lead II and Lead III type. Curve, two years later, large Q_2 and Q_3 , slurring of QRS and T_2 inversion. This patient had a heavy feeling of pressure behind the sternum on walking as little as a block or on going up one flight of stairs. This feeling completely disappeared while taking trichlorethylene three times daily, and the patient resumed his occupation at the end of three weeks. On reducing the trichlorethylene to once daily the pain returned but not as frequently as formerly. On again taking the drug three times daily there was no pain. He has changed his occupation to one of considerable mental strain, and short periods of great activity, discomfort does not occur as long as trichlorethylene is taken.

Case 16 White male, aged 59. Hypertensive arteriosclerotic cardiovascular disease. Anginal pain on moderate exertion, able to carry on occupation as insurance adjuster without great difficulty. Blood pressure, 178 systolic and 120 diastolic. Electrocardiogram Lead II and Lead III type coronary curve. No relief from immediate attacks on exhibition of trichlorethylene and attacks not lessened in frequency and severity in two weeks' trial. He refused to take this drug longer. The blood pressure was not affected. The patient obtained moderate relief with theocalcin. Patient died 20 months later, from coronary thrombosis.

Case 17 White male, aged 40. Gives history of hypertension, but this was not found at examination. Anginal type of pain, of moderate severity, not incapacitating. Blood pressure, 140 systolic and 100 diastolic. Electrocardiogram Left axis deviation. Complete prevention of pain with trichlorethylene. Neurotic personality. No history available after one month.

Case 18 White male, aged 55. Arteriosclerotic cardiovascular disease. One

year previously this patient had had an attack of severe precordial pain radiating out the left arm and lasting 48 hours. He was kept in bed for six weeks. During this time an electrocardiogram revealed low voltage, slurring of QRS waves, T_2 and T_1 inversion. An electrocardiogram six months later showed only T_1 inversion and low voltage. There had been several minor attacks preceding the severe one. Following the major attack the patient had frequent attacks daily occurring with anger, excitement or exertion, and more severe in cold weather. At time of examination the blood pressure was 120 systolic and 80 diastolic. Electrocardiogram Low voltage, otherwise normal mechanism. Complete relief in 24 hours after starting inhalations of trichlorethylene. There was no effect upon blood pressure. Patient under observation for six months at time of writing only occasional attacks of mild pain. This patient was very high-strung and irritable and he has noted a marked diminution in this irritability since taking trichlorethylene. It has been inhaled three times daily throughout the period of observation.

Case 19 Colored male, aged 41. Syphilitic aortitis, aortic insufficiency, angina pectoris. Blood pressure, 140 systolic and 60 diastolic. Trichlorethylene lessened the severity and frequency of pain to a moderate degree during a month's treatment. The patient was receiving antiluetic treatment. Electrocardiogram Left axis deviation.

Case 20 White male, aged 56. Arteriosclerotic cardiovascular disease. Coronary thrombosis five months before examination. Total disability because of recurring anginal pain on slight exertion or excitement. Blood pressure, 220 systolic and 140 diastolic. Immediate attacks at first had been relieved by amyl nitrite, which caused severe headache. Trichlorethylene prevented attacks for two months and then lost this effect, but it continued to afford relief in immediate attacks of pain. Electrocardiogram Lead II and Lead III type of coronary curve.

Case 21 White male, aged 54. Arteriosclerotic cardiovascular disease. History of coronary thrombosis two years previously, since that time retrosternal oppression on exertion or excitement. Blood pressure, 150 systolic and 90 diastolic. Lead I and chest lead type of coronary curve. Theobromine gave no relief. Trichlorethylene prevented such pain for a period of one month. No observations since this time. No effect upon blood pressure.

Case 22 White male, aged 76. Arteriosclerotic cardiovascular disease. Electrocardiogram Left axis deviation, slurring of QRS. Infected gangrene of right foot. Paroxysmal pains of anginal type occurring while in bed and persisting after amputation. Relieved by amyl nitrite. Blood pressure, 150 systolic and 100 diastolic. Frequency and severity of pain markedly diminished while taking trichlorethylene both before and after amputation. No change in blood pressure.

Case 23 White male, aged 68. Arteriosclerotic cardiovascular disease, angina pectoris. Crushing precordial pain caused by exertion or excitement, relieved by nitroglycerine. Nitroglycerine caused severe headache. Blood pressure, 150 systolic and 105 diastolic. Two weeks after trichlorethylene, blood pressure 130 systolic and 80 diastolic, no pain since drug started. Six months later at work, occasional pain much less severe than formerly. Continues to take trichlorethylene daily. Electrocardiogram left axis deviation (see footnote on page 1192).

Case 24 White male, aged 48. Hypertensive arteriosclerotic cardiovascular disease, angina pectoris. Squeezing vice-like, retrosternal pain radiating out left arm, occurring only on exertion. Known hypertensive for several years. Blood pressure, 190 systolic and 130 diastolic. Pain occurred on walking rapidly for two blocks. Electrocardiogram slurring of QRS waves, convex ST_2 , inverted T_1 . Blood pressure two weeks after trichlorethylene, 175 systolic and 105 diastolic. Estimated 20 per cent improvement. Six weeks after trichlorethylene, blood pressure 130 systolic and 85 diastolic, could walk 10 blocks rapidly. Four months later could

walk 20 blocks without pain, blood pressure, 128 systolic and 80 diastolic. Trichlorethylene discontinued. Returned in three weeks with blood pressure 140 systolic and 100 diastolic and occasional return of pain. Again the pain was prevented by trichlorethylene inhaled three times daily and patient continues to take this drug, varying the frequency of inhalation from one to three times daily according to the return of pain.

Case 25 White male, aged 76. Arteriosclerotic hypertensive cardiovascular disease, angina pectoris. Heavy oppression in chest on slight exertion such as walking one-half block up slight grade. Relieved by amyl nitrite, but this drug caused headache. Trichlorethylene failed to relieve immediate attacks of pain. Blood pressure, 170 systolic and 105 diastolic. Electrocardiogram. Left axis deviation, slurring of QRS waves. Trichlorethylene used for two weeks, discontinued because it produced unconsciousness at times and this caused the patient great anxiety. There had been no effect upon the pain. Blood pressure at the time of the drug's discontinuance 180 systolic and 110 diastolic.

Case 26 White male, aged 57. Chronic nephritis, tumor of urinary bladder, generalized arteriosclerosis, angina pectoris, uremia. Anginal pain of one year's duration. At time of initiation of treatment pain was caused by the slightest exertion such as getting out of bed. Trichlorethylene one ampoule by inhalation thrice daily. In one week he was able to be up and move about ward. At this time exercise tolerance over standard portable steps equaled two round trips. At end of second week he was able to make seven or eight round trips. Electrocardiogram. Left axis deviation. Patient died, uremic coma, at end of third week. Anatomical diagnosis: chronic cystitis, bilateral chronic nephritis, generalized arteriosclerosis, coronary sclerosis, fibrosis of apex of right ventricle, fulguration necrosis of bladder wall.

Case 27 White male, aged 50. Arteriosclerotic cardiovascular disease, angina pectoris. One year previously this patient had suffered from a coronary occlusion. The electrocardiogram at that time was of the Lead I, chest lead type of acute coronary occlusion curve. Following the above illness the patient never was able to return to his occupation of executive because of recurring seizures of angina pectoris. Five weeks before death the patient became bedridden, precordial pain occurring in severe seizures while at rest. Theobromine derivatives were of help in diminishing the frequency and severity of attacks. The patient was given inhalations of trichlorethylene three times daily and inhalations for immediate attacks over a period of three weeks without appreciable benefit. Nitroglycerine failed to relieve the pain. He died in a prolonged attack of pain during which the electrocardiogram revealed a Lead III type of acute coronary curve.

I can offer no adequate explanation of why this drug is effective in preventing attacks of angina pectoris. The fall in blood pressure at times noted may be a factor in some cases, but obviously cannot explain the greater number of cases in which no such reaction has taken place. No constant effect upon coronary circulation has been shown to occur. There is no evidence that conduction of nerve impulses is impaired. There is definite evidence that this drug has sedative and anesthetic properties. A few unrelated observations have been made upon pain due to other causes, and in the cases so treated a sedative and hypalgesic action has been noted. In the case histories it is frequently stated that the patients are of high-strung, nervous temperament. The hypalgesic and sedative action of this drug is the only explanation of its effectiveness in preventing and relieving angina pectoris with any evidence in its favor at this time.

SUMMARY AND CONCLUSIONS

1 The inhalation from two to four times daily of ampoules of trichlorethylene, containing 1 c c, has been used with some success in the prevention of attacks of angina pectoris. However, this series is not sufficiently large to warrant too favorable conclusions, since in any small series there may be a considerable distortion due to the element of chance.

2 While pure trichlorethylene in the recommended dosage does not seem to be toxic, nevertheless, because of the reported cases of industrial poisoning due to this agent, it should be used with some caution.

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CASE REPORTS

TREATMENT OF HEMOLYTIC STREPTOCOCCIC MENINGITIS WITH PARA-AMINO-BENZENE-SULFONAMIDE, REPORT OF A CASE, WITH RECOVERY

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THE observations of European investigators and more recently of Long^{1,2} and Schwentker³ in this country on the treatment of beta hemolytic streptococcal infections by para-amino-benzene-sulfonamide suggested to the author the use of this drug in infections of the central nervous system. The opportunity presented itself to try this drug on a case of fulminating meningitis following a middle ear and mastoid infection admitted to the Neurosurgical Service of Dr. Charles Bagley, Jr., at the University of Maryland Hospital on December 18, 1936. The dosage used in the treatment of this case was the same as that used by Schwentker³ in a similar case treated by him several weeks previously. It seems worthwhile to make this preliminary report of a single case because of the striking therapeutic results. The rapid recovery of a patient suffering from a disease which is practically always fatal strongly suggests that the treatment employed may have had a specific effect.

CASE REPORT

History On December 5, 1936, the patient, a white female 28 years of age, began to have earache in the right ear. Later that evening the ear began to discharge followed by some relief from pain, but the pain continued somewhat until about December 12. From December 12 to December 17 she seemed much improved. On December 16 she went to bed feeling quite well, but was awakened at 3:00 a.m. with severe headache. By morning she had become very confused and drowsy. Her father stated he was "unable to get anything out of her." Her family physician took her to the Frederick City Hospital on December 17 where she was seen by Dr. A. A. Pearre. There a diagnosis of meningitis was made clinically and examination of the cerebrospinal fluid on December 17 showed 3880 cells with 79 per cent polymorphonuclears. No bacteria were seen in the smear. Examination of the blood revealed a white cell count of 29,600. The following morning she was admitted to the Neurosurgical Service of Dr. Charles Bagley, Jr., at the University Hospital. While the patient was being transferred from Frederick to Baltimore, Dr. Pearre called and stated that the spinal fluid culture taken the day before was positive for *Streptococcus hemolyticus*. The past history was negative.

Examination On admission the patient appeared critically ill. The skin was flushed and hot. She was unresponsive and reacted only to painful stimuli. There was a yellowish watery discharge from the right ear. No swelling over mastoid or ear. Divergent strabismus. Deep reflexes equal and hyperactive. Kernig positive.

* Presented before the Neuropsychiatric Section of the Baltimore City Medical Society, January 14, 1937.

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Abdominals diminished Bilateral plantar extensor response Rigidity of neck with mild opisthotonos Hearing reduced in left ear (since childhood) Peripheral facial paralysis on right side

On December 22, 1936, the examination of the blood was as follows Hemoglobin 100 per cent, r b c 4,400,000, w b c 5600, polymorphonuclears 89 per cent, lymphocytes 10 per cent, large mononuclears 1 per cent Blood non-protein nitrogen 27 mg per cent, blood sugar 114 mg per cent Wassermann reaction negative On December 26 the white blood cells were 20,000, polymorphonuclears 88 per cent, lymphocytes 10 per cent, large mononuclears 2 per cent Sedimentation rate 34 mm in one hour On January 5, 1937 the white blood count was 11,000 The blood culture of December 18, 1936, was negative after five days A smear of the pus taken from the ear on December 19 revealed pus cells polymorphonuclears predominating, together with gram-positive diplococci and streptococci A culture of this pus showed *Staphylococcus aureus* Urine examinations were entirely negative on December 26, January 1, and January 6 The findings in the spinal fluid are cited below

Course On admission to the hospital the patient was very stuporous The temperature was 105.4° F (R) A mastoid infection was considered likely because of the peripheral facial paralysis but it seemed useless to consider operation Examination of the spinal fluid in the Frederick City Hospital on December 17, 1936, had shown a pleocytosis of 3880 cells per cu mm and a positive culture for hemolytic streptococci Immediately upon admission late in the afternoon of December 18, the spinal fluid was found to be cloudy, contained 5181 cells, and was under a pressure of 333 mm of water The next morning the culture from this fluid showed a heavy growth of beta hemolytic streptococci In the afternoon of December 19, a second puncture was done and the fluid was found to be under a pressure of 440 mm of water Twenty-five cubic centimeters of fluid were withdrawn and 20 c c of 0.8 per cent para-amino-benzene-sulfonamide in normal saline solution were injected intraspinally Following this a subcutaneous injection of 200 c c of the same drug was given Treatment was continued from this point on as described in a later section and summarized in table 1

On December 20, twenty-four hours following the administration of the drug, the temperature dropped to 104° F and there was a striking decrease in the spinal fluid cell count from 5181 to 1026 The pressure also dropped from 440 to 240 mm of water The patient was able to take fluids by mouth, smiled occasionally, but was still drowsy and disoriented Once or twice she inquired about her surroundings, but late in the evening she again became very unresponsive

On December 21, the temperature dropped to 102° F (R) and the patient seemed slightly improved In the afternoon she became more confused and resistive She muttered to herself frequently The spinal fluid pressure was 110 mm of water, contained 1134 cells, and the culture was still positive for *Streptococcus hemolyticus*

On December 22 she refused food She became moderately cyanotic and the respiratory rate increased to 40 She was very noisy and cried out frequently The spinal fluid pressure was 90 and the cell count dropped to 600 In previous cultures the organisms grew out overnight, but the culture taken on this day showed a very sparse growth in 36 hours

On December 23, she was more cooperative but was still mildly disoriented The temperature dropped to 99.4° F (R) A bloody tap was obtained on doing the spinal puncture A smear was made from the fluid and showed a few gram-positive cocci, but the culture was sterile A transfusion of 300 c c of blood was given without reaction The respiratory rate continued around 40 At no time during her course had there been swelling over the mastoid process, but in view of the general improvement, it was felt wise to consider doing a mastoidectomy Roentgen-ray of the mastoids was done and Dr H J Walton reported "moderate clouding of

TABLE I
Chart Showing Cerebrospinal Fluid Findings and Record of Treatment

Day of disease	3	4	5	6	7	8	9	10	11	12	13	14	15	16	18	19	20	22	28
Day of month	(Dec) 17	18	19	20	21	22	23	24	25	26	27	28	29	30	(Jan) 1	2	3	5	11
Cerebrospinal Fluid Cell count	3880	5181	—	1026	1134	600	Bloody tap	—	450	325	385	309	78	80	79	75	—	37	40
Culture	Positive	Posi- tive	—	Posi- tive	Posi- tive	Sparse growth	Smear pos no growth	—	Nega- tive	Nega- tive	Nega- tive	Nega- tive	Nega- tive	Nega- tive	Nega- tive	Nega- tive	—	Nega- tive	Nega- tive
Pressure (mm of H ₂ O)		330	440	240	110	90	—	110	300	118	200	220	195	175	140	110	—	175	155
Treatment (para- amino benzene sulfonamide) Oral (gm)					6	6	6	4	4	4	4	4	4	4	4	4	4	—	—
Subcutaneous (0.8% solu- tion) (c c)			200	350					—	—	—	—	—	—	—	—	—	—	—
Intraspinal (0.8% solu- tion) (c c)			20	35	15	35	18	35	20	28	25	—	—	—	—	—	—	—	—

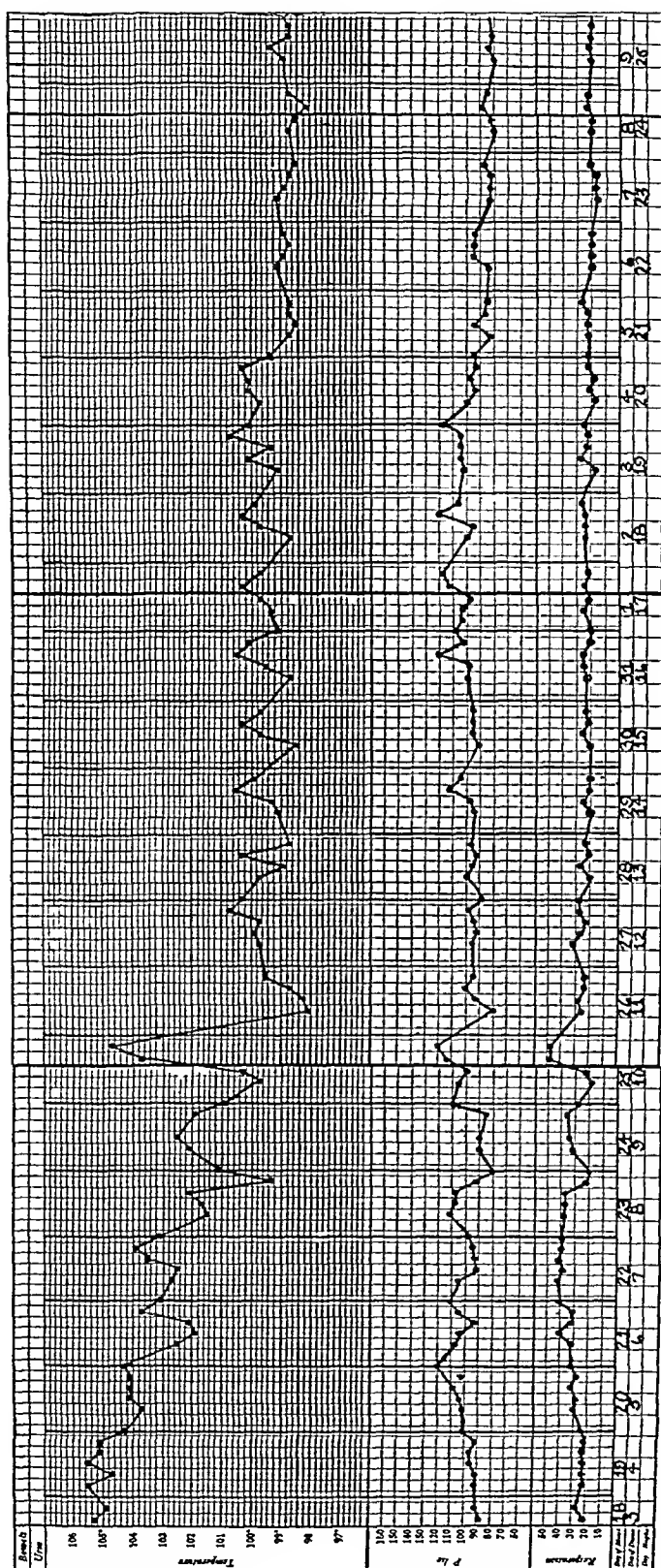


Chart of the temperature, pulse and respiration during the course of hemolytic streptococcic meningitis

the cells in the right mastoid process, suggestive of an infection. There is no indication of breaking down of the cell partitions." His impression was "mastoiditis, probably acute."

On December 24, the temperature again rose to 102.4° F (R). In the afternoon Dr. E. A. Looper did a right semi-radical mastoidectomy. The mastoid was found to be necrotic and filled with pus. The mastoid cells were curetted and the antrum opened widely. The ossicles and drum were removed. The dura was exposed above and the lateral sinus below. The patient stood the procedure well. It is of great interest to note that the spinal fluid had become sterile on the previous day.

On the following morning, December 25, the temperature dropped to 99.6° F. Her condition was definitely improved. She was more alert and talked with visitors. In the afternoon a second transfusion of 300 cc was given. She had a reaction following this and the temperature rose to 104.6° F (R). The right ear and mastoid were draining profusely. The spinal fluid cell count was 450, pressure 300 (patient struggling), and culture of the spinal fluid was negative. Slight cyanosis of the skin was still present.

On December 26, her color was improved and respirations were slower. She was able to feed herself, talked coherently, and was definitely more alert mentally. She talked with her visitors and seemed cheerful. The temperature dropped to 98.4° F (M) and the cell count to 325.

From this time on her improvement was steady. Between December 26 and January 4, the temperature ranged between 98.4° F (M) and 100.6° F (M). The medication was discontinued on January 3, and on January 5 the temperature dropped to a normal level. Between January 5 and January 12 the temperature rose to 100° F (M) on two occasions. The cell count dropped to 40 on January 11. Ten consecutive cultures of the spinal fluid were sterile. Since January 8, she has been allowed out of bed.

Examination on January 11 showed her to be bright and mentally alert. Her father could see no change in her mental acuity. The peripheral facial paralysis on the right side noted on admission was still present. The deep reflexes were all hyperactive, with bilateral ankle clonus. The plantar responses were equivocal. The fundi were normal.

Treatment. Between December 19, 1936, and December 27 the patient received nine intraspinal injections of 0.8 per cent para-amino-benzene-sulfonamide in amounts ranging from 20 to 35 cc, depending upon the amount of fluid withdrawn. On December 19 and 20, respectively, 200 cc (1.6 gm) and 350 cc (2.8 gm) of 0.8 per cent para-amino-benzene-sulfonamide were injected subcutaneously.

On December 21, 22, and 23, 6 gm of the substance were given in the form of "Prontylin" tablets by mouth, 3 tablets six times a day. From December 24 to January 3 she was given 4 gm every 24 hours, or 3 tablets four times a day.

As yet the optimum dosage of this drug* in the treatment of beta hemolytic streptococcal infections is undetermined. Long feels that large doses should be given in the first few days of treatment. He has found that patients tolerate a dose of 1 gm per 20 lb of body weight every 24 hours for as long as a month. He has pointed out that the drug administered orally should be given in divided doses over a 24-hour period.

In this case, four intraspinal injections were given after the spinal fluid became

* The crystalline para-amino-benzene-sulfonamide used was made by the Du Pont Chemical Company, and the "Prontylin" tablets by the Winthrop Chemical Company. Two derivatives of para-amino-benzene-sulfonamide are on the market under the name of "Prontosil" solution and "Prontosil" tablets. Prontosil solution may be used for subcutaneous injections but not intraspinally, for Schwentker³ has found that Prontosil solution increases the cellular reaction in the leptomeninges and is therefore more irritating than solutions of para-amino-benzene-sulfonamide. For further discussion of these derivatives the reader is referred to Long's paper.¹

sterile, and the drug was continued by mouth for 11 days after obtaining a sterile spinal fluid

In the preparation of the powdered para-amino-benzene-sulfonamide for parenteral and intraspinal injection, sterile normal salt solution was brought to a boil and the powder slowly dropped in. Long has found that no further sterilization is necessary. The solution should be prepared just before using.

Comment As with any new drug, the therapeutic value of this new chemotherapeutic agent can be determined only after prolonged use. In this one case, however, it appears that para-amino-benzene-sulfonamide produced a powerful bacteriostatic effect in a fulminating case of beta hemolytic streptococcal meningitis. Twenty-four hours after the injection of 1.6 gm subcutaneously and 0.016 gm intraspinally the spinal fluid cell count dropped from 5181 to 1026. Throughout the course there was a steady decrease in the cell count and on the tenth day following treatment the cell count had dropped to 78 and on the twenty-second day to 40.

The cerebrospinal fluid pressure before treatment was 440 mm of water. Within 24 hours, the pressure dropped to 240 mm of water, and thereafter did not exceed 200 mm except on one occasion when the patient was straining during the puncture, when it was found to be 300.

Before treatment, the spinal fluid cultures were found to be positive for beta hemolytic streptococci, both in the Frederick City Hospital and at the University Hospital. For two days following the institution of treatment, cultures of the organism grew out promptly within 24 hours. On the third day following treatment, the growth became sparse and required 36 hours. On the fourth day a few gram-positive cocci were found in the smear, but the culture was sterile. Following this, 10 consecutive negative cultures were obtained. This behavior of the spinal fluid cultures is further evidence of the bacteriostatic power of the drug on beta hemolytic streptococci. This marked reduction in cell count corroborates Schwentker's finding³ that the drug itself produces no cellular response in the leptomeninges. Furthermore in this case, the inflammatory reaction of the leptomeninges was greatly decreased after one intraspinal injection.

Because of the existing peripheral facial paralysis at the time the patient was admitted to the hospital, it was felt that she had a mastoid infection and that the portal of entry was through the mastoid, even though there was no swelling in the region of the mastoid. Because of the heretofore hopeless outcome of streptococcal meningitis, it was thought best to see if the patient responded to the drug before subjecting her to a mastoidectomy. That the drainage of the mastoid bore no relation to the decrease in meningeal reaction is shown by the fact that the spinal fluid cultures became negative on December 23, twenty-four hours before the mastoidectomy was performed. This operation was considered worthwhile at this time only because of the striking improvement in the patient's general condition.

In the treatment of streptococcal meningitis with this drug, the exact required dosage is as yet undetermined. The dosage given this patient seemed to be adequate and until further data are forthcoming it is suggested that the intraspinal injection be continued until three consecutive negative cultures are obtained, and that the oral administration be continued for 10 days following the last positive spinal fluid culture. As pointed out by Long, unless the drug is given for a sufficient length of time there may be a relapse of the infection.

Whether or not parenteral and oral administration of the drug will control infection in the central nervous system without intraspinal injection has not yet been determined

The drug is relatively non-toxic but two complications, sulphemoglobinemia and acidosis, are occasionally encountered. Should either occur, the drug should be discontinued or the dosage decreased for 24 to 48 hours. Acidosis may be relieved by parenteral injection of 5 per cent sodium lactate.

I wish to express my appreciation to Dr. Perrin H. Long and Dr. Francis F. Schwentker for supplying me with the drug and for their suggestions in the treatment, to Dr. Charles Bagley, Jr., for permission to publish the case, and to Dr. N. Davidson for his assistance in treating the patient.

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INTERMITTENT HYPERTHERMIA OF SEVEN YEARS' DURATION

By EDGAR V. ALLEN, M.D., F.A.C.P., *Rochester, Minnesota*

A MECHANICAL engineer, 38 years old, was admitted to the Clinic September 27, 1935, complaining of attacks of fever during a period of seven years. The patient was born in Dayton, Ohio, and moved to southern California at the age of eight years. He had never been in the tropics, in South or Central America or in Mexico other than in parts within 50 miles of the California border. He had had measles and whooping cough as a child, and while serving in the Navy in 1918 had had measles complicated by lobar pneumonia.

Between the ages of 23 and 35 he had had severe frontal headaches associated with photophobia, but without nausea and vomiting. In 1926 repeated washing of both antrums relieved the headaches markedly but not completely. In 1928, at the age of 31, he had an attack of influenza characterized by malaise, fever and weakness. There was no associated somnolence or insomnia. About six weeks later he experienced the first of the attacks of fever, which attacks had occurred intermittently ever since.

The attacks of fever varied greatly in intensity (figure 1). They were preceded by prodromal symptoms by as much as 24 to 48 hours, such symptoms consisting of aching in the neck, shoulders, small of the back and feet and ankles, and often in the hands and wrists. Chilliness, and often severe chills, were experienced. Occasionally nausea and vomiting occurred as the temperature of the body increased. When the temperature reached the maximum, the patient perspired profusely and his temperature then began to decrease. Usually he slept during the time his temperature was returning to normal. He would lose from four to seven pounds (1.8 to 3.2 kg.) during such attacks.

* Read before the meeting of the Minnesota Society of Internal Medicine, Duluth, Minnesota, June 6, 1936.

From the Division of Medicine, The Mayo Clinic, Rochester, Minnesota.

Twenty-four hours after an attack the patient felt entirely well. In later years, severe chills and nausea which had formerly almost invariably accompanied episodes of fever had become very rare, and aching of the legs, which had occurred as a prodromal symptom in the earlier years, had been replaced by aching of the feet and ankles. Aching in the neck, shoulders and small of the back had occurred with the attacks only in the past three or four years. The attacks had gradually increased in

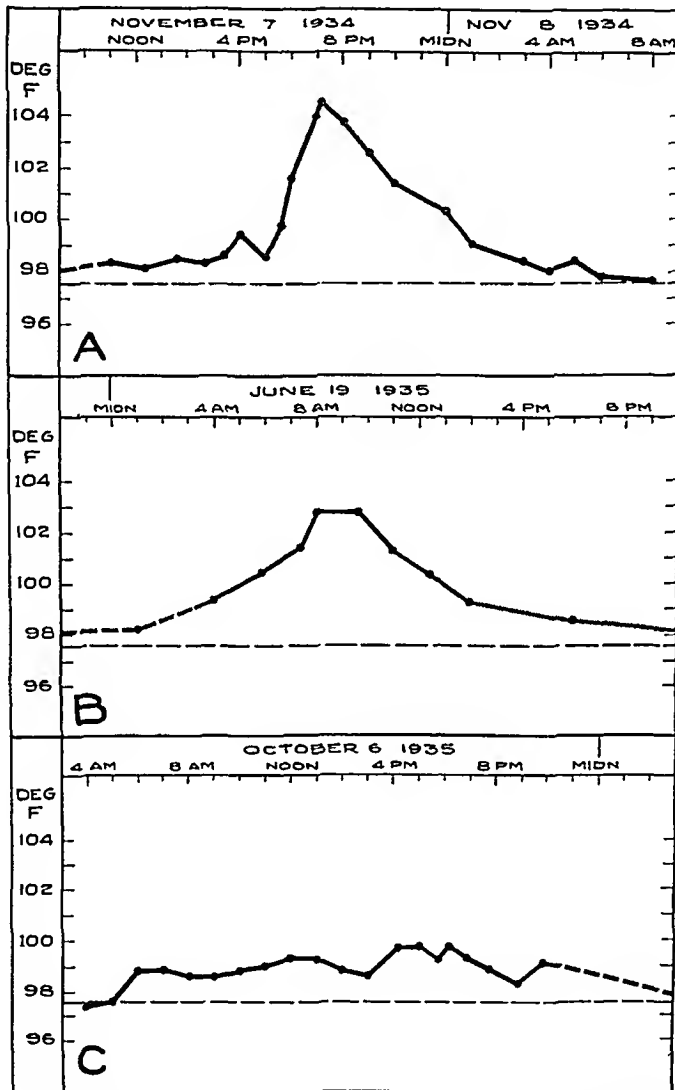


FIG 1 The inconstancy of the response shown by charting the temperature of the body during three (A, B and C) spontaneous attacks of fever

number from about 10 in 1929 to 46 in 1935. The average of numerous determinations of body temperature between episodes of fever was roughly 97.6° F. The longest interval in which no attack had occurred had been 100 days, in 1933. Complete records had been kept in 1934 and 1935, and during this time the longest interval between attacks was 15 days and the shortest, six days. The mild and severe attacks occurred with no regularity, there being no relationship between the intensity of attacks and the interval between them (figure 2).

During the six years prior to examination at the Clinic the patient had been under the supervision of a number of physicians, but their examinations had always given essentially negative results. Agglutination tests for undulant fever, examination of the blood for malarial organisms and spirochetes, urinalyses, and various roentgenologic examinations, had always been negative. Neoarsphenamine (given

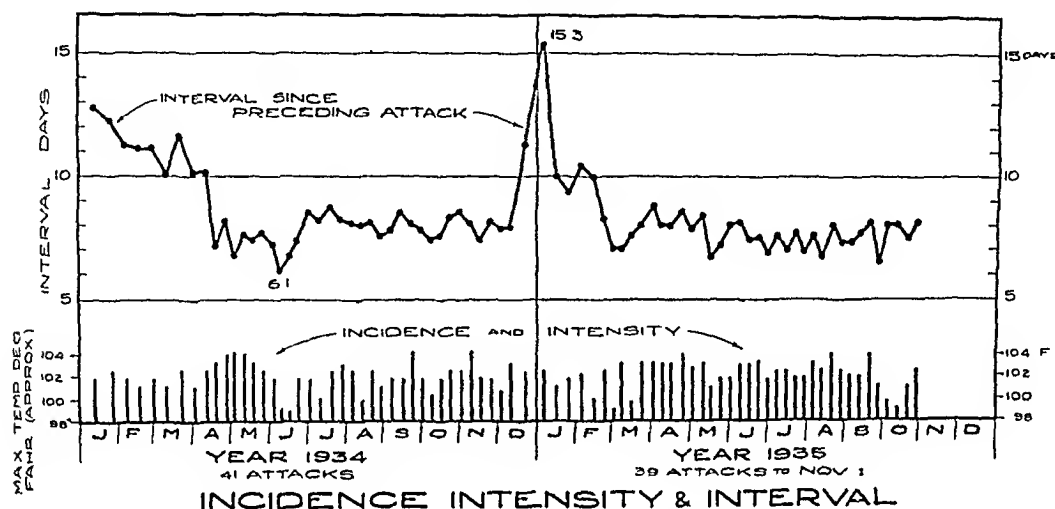


FIG 2 The upper part of the chart indicates the intervals between attacks during 1935 and 1936, the shortest interval between episodes of fever was six days, the longest 15 days. The temperatures attained during attacks, which varied from 98.8° to 104.4° F, are shown in the lower part of the chart.

intravenously four times at weekly intervals), oxyquinoline sulphate (given in retention enemas and by mouth for several months) and quinine sulphate (in amounts of 20 grams [13 gm.] during the prodromal stages of three attacks), had been without benefit. Two brands of acetylsalicylic acid (empirin and aspirin) have been found to lower the body temperature substantially, although the fever persisted over a longer period when these drugs were taken.

Physical examination at the Clinic revealed small tonsils and evidence of sinus infection. No evidence of any abnormality was found on examination of the heart, lungs, abdomen, lymph nodes, and extremities, or prostate gland, seminal vesicles, and epididymides. A complete neurologic examination also gave negative results. Proctoscopic examination showed nothing significant. Examination of the eyes was negative except for evidence of old choroiditis on the nasal side of the right macula and a small opacity near the periphery of the lower nasal quadrant of the right lens. The blood pressure in millimeters of mercury was 100 systolic and 70 diastolic. Routine examination of the urine and blood, including determination of the values for hemoglobin and blood urea, enumeration of erythrocytes, examination of blood smears, and a serologic test for syphilis, were all negative. Leukocytes numbered 8,300 per cubic millimeter of blood, of which 46 per cent were lymphocytes, 6 per cent monocytes, 46 per cent neutrophils and 2 per cent eosinophils. Bronchoscopic examination failed to reveal any evidence of bronchiectasis. Visualization of the kidneys following the intravenous injection of neo-iodopax showed them to be entirely normal. Agglutination tests of the blood for *Pasturella tularensis* and *Brucella abortus* were negative. A tuberculin test was positive. Roentgenologic examination of the sinuses disclosed markedly thickened membrane in the right antrum, and that of the teeth some evidence of infection in one tooth. There was no growth of organisms on culture of the urine. Cultures from the nasopharynx revealed streptococci,

and those of prostatic secretion both streptococci and staphylococci. The sedimentation rate of erythrocytes was 5 mm in one hour.

The patient was then observed in the hospital during an attack of fever. His temperature rose from 97.2° to 100.4° F in eight and a half hours, and then decreased to 97.6° F in three and a half hours. The pulse rate increased to 120 beats per minute. Urine, passed when the temperature was 101° F, was normal. Examination of blood smears for malarial organisms, spirochetes and trypanosomes was likewise negative at this time. Leukocytes numbered 20,000 per cubic millimeter, 28 per cent being lymphocytes, 3 per cent monocytes, 67 per cent neutrophils, 1 per cent eosinophils and 1 per cent basophils, there was evidence of moderate toxicity of the leukocytes. The sedimentation rate was 7 mm in one hour. Spinal puncture, made when the temperature was 101.0° F, showed normal pressure responses, analysis of the spinal fluid gave negative Wassermann, Kline and Nonne reactions and revealed 3 small lymphocytes per cubic millimeter, the total protein being 30 mg and the colloidal gold curve 0 111 100 000. Blood cultures on brain broth and on blood agar were negative.

On October 2 the infected tooth was removed, cultures from the root revealing streptococci. Because washings from the right antrum were purulent and contained streptococci and because the left antrum appeared to be involved in a similar manner, bilateral antral windows were made on October 8, 1935. On November 27 and 28 roentgen treatment* was given to the right and left sides of the head respectively. On November 2, subcutaneous injections of a vaccine made from organisms cultured from the nasopharynx were begun, injections being given twice weekly for five weeks in increasing doses, and subsequently in constant doses every week. None of these procedures influenced the recurrence of attacks in any way.

The patient was observed during several spontaneous attacks of fever. Possibility of malingering was excluded by constant observation and by use of an automatic rectal thermometer. During an episode of spontaneous fever 1/6 grain (0.01 gm) of pilocarpine was administered hypodermically, profuse salivation and sweating followed but the fever was not influenced in the ensuing hour. Three grains (0.20 gm) of sodium amytal administered by mouth then induced sound sleep although the fever was unaffected (figure 3A). At another time phenobarbital given in sufficient amount to cause somnolence did not prevent or modify an attack. During a subsequent attack ergotamine tartrate was given subcutaneously in amounts of 0.25, 0.25, 0.25, 0.25 and 0.50 mg, respectively, at hourly intervals, the course of the fever was unchanged (figure 3B). The temperature response to intravenously injected typhoid vaccine (figure 3C) was about the same as that observed during spontaneous episodes of fever (figure 3D). The response of body temperature to increased environmental temperature in a Simpson-Kettering fever cabinet and in a full-length body baker was considered normal (figures 3E and F). During a spontaneous attack, when the oral temperature was 102.0° F, 1/4 grain (0.016 gm) of morphine sulphate was given subcutaneously. The temperature increased another degree in the next hour, and remained at this height for two hours when spontaneous sweating set in and the temperature dropped (figure 3G). Although the patient slept during this period, no influence on the course of the fever was noted. In another attack amidopyrine was administered three times, in amounts of 10 grains (0.65 gm) at hourly intervals. The first dose induced some sweating and momentarily suspended the rise of the fever, after the second dose moderate sweating continued and the fever dropped, but not until nine hours later did it reach the individual normal of 97.6° F (figure 3H). During another spontaneous attack 15 grains (1.0 gm) of "Iarodon" (Hoffman-La Roche, Inc) was given by mouth when the oral temperature reached 100.0° F, an equal amount was given an hour later. The temperature only slightly exceeded

* 135 kilovolts, 16 inches, 5 milliamperes, 6 mm aluminum filter, 20 minutes

100° F and returned nearly to normal in seven hours, the fever recurred, however, eight hours later, and 15 grains of larodon was again given. Some effect on the temperature was again noted, but it did not become normal until 13 hours after the last (29 hours after the first) administration of larodon (figure 3I). These results

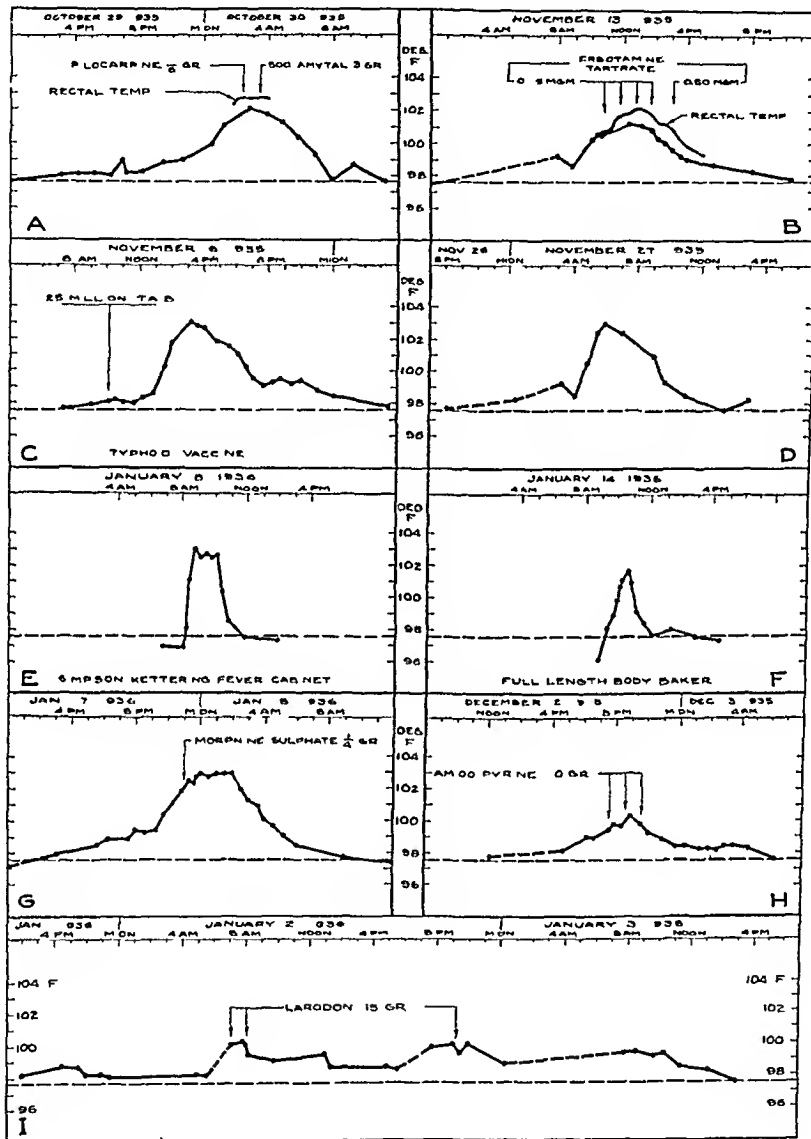


FIG 3 A, B and G illustrating the absence of effect of pilocarpine, sodium amytal ergotamine tartrate and morphine sulphate on the fever, H and I, the effects of amidopyrine and larodon in decreasing the fever, C, fever induced by injecting typhoid vaccine intravenously, which simulated closely that occurring spontaneously D, E and F, the response of the body temperature to increased environmental temperature, which was considered normal

were similar to those sometimes noted by the patient on using acetylsalicylic acid (empirin and aspirin) prior to coming to the Clinic

Typhoid vaccine was injected intravenously November 16, 18 and 30, and December 2 and 4 in amounts of 25, 40, 60, 85, and 120 millions of killed organisms,

respectively. On each occasion the oral temperature was elevated to between 102.7° and 103.3° F. The reactions, including symptoms and fever, were identical to those noted during spontaneous attacks of the same degree of fever. Spontaneous attacks of fever were experienced on November 27 and December 12. The first occurred on the ninth day after an injection of typhoid vaccine and on the fourteenth day after the preceding spontaneous attack, the second spontaneous attack occurred on the eighth day after an injection of typhoid vaccine and on the sixteenth day after the preceding spontaneous attack. Spontaneous attacks then occurred December 18 and 24, and on January 2, or at intervals of approximately six days. These results suggested that the fever induced by the intravenous injection of typhoid vaccine served as a substitute for the spontaneous attack, inasmuch as an interval of 14 or 15 days between spontaneous attacks had occurred only once in the last two years.

In the hope that fever induced artificially by any means would substitute for spontaneous attacks, on the sixth day after a spontaneous attack the body temperature was elevated to 103.0° F by mouth (103.4° F by rectum) and was kept at or near this level for an hour in a Simpson-Kettering fever cabinet. One day after this fever treatment, or seven days after the spontaneous attack, moderate spontaneous prodromes appeared and persisted for about two days, but no fever was observed. Five days after this fever treatment, or 12 days after the preceding spontaneous attack, the temperature was raised to 101.7° F (by mouth) in an ordinary full-length baker and was kept there for a few minutes. A spontaneous attack occurred four days later, or 15 days after the preceding spontaneous attack and nine days after the fever artificially induced in the fever cabinet. This suggested that the higher temperature maintained for an hour in the fever cabinet served as a substitute for a spontaneous attack and showed definitely that the lower temperature attained in the body baker for a short period did not so substitute. It should be noted that the total "fever area" in the first instance was over twice as great as in the second.

During another attack of fever, three injections of 9 minims (0.5 c.c.) each, of epinephrine were given at hourly intervals without effect on the fever. Another episode of fever occurred while the patient was taking phenobarbital, which made him very drowsy, 1 c.c. of pituitrin injected subcutaneously and 20 c.c. of whole blood injected intramuscularly did not influence the fever.

On February 3, 1936, Dr. E. C. Rosenow began a study of the patient from a bacteriologic standpoint. Blood agar platings of material from the nasopharynx and of pus expressed from the tonsils revealed unusually large numbers of green-producing streptococci. The cataphoretic velocity of these streptococci was normal. Skin tests made with the euglobulin fraction of the blood serum of horses, injected for immunization purposes with neurotropic and arthrotropic types of organisms, revealed a marked reaction in each instance, apparently indicating antigen of these organisms in the skin. Administration to the patient of the serum of horses so treated, on three successive days, greatly diminished this skin reaction, indicating, apparently, almost complete neutralization of the antigen in the patient's skin, although an attack of fever occurred at the expected time.

At this time the leukocytes numbered 7,400 per cubic millimeter of blood, 84 per cent of them being neutrophils, 7 per cent monocytes and 9 per cent lymphocytes. The sedimentation rate was 7 mm. in one hour. On February 9 serum sickness began, this was characterized by a temperature as high as 103° F, and by urticaria, chilly sensations, drowsiness and somnolence and generalized aching and erythema. The hands and feet were hot and swollen, the hands felt "asleep" at times, and there was slight aching of the eyes and head. The symptoms mentioned were moderately acute for three days and recovery was not complete for about a week after the symptoms began.

Tonsillectomy was performed February 13. Culture of the tonsils revealed the

same type of organism shown previously to be present in the nasopharynx and secretion from the tonsils. Two days after tonsillectomy another attack of moderate fever was experienced and, the following day, the fever was associated with acute bronchitis, this, however, disappeared rapidly.

The patient left our supervision on February 19, in order to return to his home, and his subsequent condition was reported by letter. He remained well. His physical and mental energy increased, he slept better, and in general his health was substantially improved over that of the preceding few years. Episodes of fever did not occur. In May, however, he wrote that intermittent nasal discharge, photophobia, and headache indicated sinus infection. His diagnosis seemed well founded, for on June 30 (136 days after the last episode and 137 days after tonsillectomy) a severe febrile episode occurred. This could hardly be a spontaneous remission since the longest interval between attacks in seven years had been 100 days and the longest interval in the preceding two years had been 15 days. After recovery from the attack just mentioned a physician confirmed the diagnosis of frontal sinusitis and non-surgical treatment was begun. Attacks of fever occurred at intervals of 68, 25, 14, 25 and 13 days.*

COMMENT

It was apparent from the history of this patient's illness that an etiologic basis for the recurrent attacks of fever would be difficult if not impossible to establish. This assumption was strengthened by the paucity of findings from examinations elsewhere and from routine examinations at the Clinic. The patient, however, was cooperative and was desirous of obtaining a cure for his condition, regardless of the length of time required or the inconveniences which such an intensive investigation would entail. The possibility that the patient was malingering was eliminated promptly by observing him during episodes of fever and by personally determining his oral and rectal temperature. The elevation of the pulse rate was further evidence that the fever was real.

The first diseases to be considered were malaria, bronchiectasis, pyelitis or pyelonephritis, bacilluria, Hodgkin's disease, undulant fever, filariasis, trypanosomiasis, spirochetosis, tularemia and the blood dyscrasias. No evidence of any of them was found. A transcription of the patient's record was subsequently sent to Colonel Charles F. Craig, Director of the Department of Tropical Medicine at Tulane University, in the faint hope that the patient might have some unusual tropical disease with which we were unfamiliar. Colonel Craig kindly reviewed the record and replied that he was quite certain that the condition was not one of tropical infection.

The next step was elimination of obvious foci of infection, although there was little hope that such a procedure would influence the attacks of fever. When the surgical treatment of infected antrums and extraction of an infected tooth were unavailing, it was apparent that the situation was a difficult one and that investigation along the lines reviewed and discussed by Dr. H. A. Reimann, of the University of Minnesota School of Medicine, should be carried out. The possibility of a psychogenic fever was promptly eliminated by failure of morphine and amytal to influence the fever reactions. Further, an attempt was made to influence the fever by roentgen irradiation of the head, after considering the possibility that the fever was of central origin and was caused by a disturbed heat-regulating center. No results were obtained by these measures and in desperation an attempt was then made to eliminate the spontaneous at-

* At this time (January 15, 1937) the patient is experiencing episodes of fever of about the same type as before tonsillectomy was performed.

tacks of fever by inducing it artificially. While the results of this procedure were valueless from a preventive standpoint, there was considerable but not conclusive evidence that artificially induced fever substituted for the spontaneous attacks. Finally, further consideration was given to the possibility that the fever was of infectious origin. Reimann has reviewed evidence that fever of infectious origin responds to antipyretic drugs, while normal temperatures and psychogenic fevers do not. Our studies indicated that the antipyretics, amidopyrine and "larodon," definitely influenced the fever, whereas pilocarpine, ergotamine tartrate, morphine, amytal and epinephrine did not. These results suggested that the fever was produced by infection. This was further suggested by an increase in the number of leukocytes per cubic millimeter of blood and an increase in the percentage of neutrophils on one occasion, and by an increase in the percentage of neutrophils without an increase in the number of leukocytes during fever on another. Dr. Reimann then reviewed our study records and reported that he believed the fever was quite definitely of infectious origin, probably from some focus of infection.

It is interesting that there was no significant increase in the sedimentation rate. However, Reimann has pointed out that failure of the speed of sedimentation to increase during fever does not exclude an infectious origin. Because of the possibility of some hidden focus of infection, Rosenow's hyperimmune streptococcus antiserum was given, but an attack of spontaneous fever occurred at the expected time. Serum sickness followed the administration of horse serum, and before a sufficient interval had elapsed to determine whether or not another episode of fever would follow, tonsillectomy was performed because the tonsils were the only remaining possible focus of infection. Much to our surprise attacks of fever did not occur subsequently while the patient was under our observation, and he has reported that none occurred for four and a half months after his dismissal from the Clinic. He reported further that his general health had improved greatly. The evidence is quite clear, therefore, that either serum sickness or tonsillectomy produced the good therapeutic results. The former assumption appears quite untenable, and there can be no reasonable doubt but that the organisms in the tonsils were responsible for the recurrent attacks of fever. A return of episodes of hyperthermia after the longest free interval in seven years was definitely associated with frontal sinusitis. It seems fairly certain, therefore, that the episodes of hyperthermia were of infectious origin and that the organisms responsible for them lodged in the tonsils and sinuses.

SUMMARY

Study of a patient who had recurrent episodes of hyperthermia for seven years indicated that his fever was of infectious origin. Tonsillectomy produced temporary cessation of these attacks of fever when all other methods of treatment which were tried had been without avail. Recurrence of attacks was associated with frontal sinusitis.

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PRIMARY CARCINOMA OF THE LIVER WITH BONE METASTASIS

By HERMAN BOLKER, M D , MENDEL JACOBI, M D , and MORRIS T
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PROVED cases of primary carcinoma of the liver are few in number, particularly so in comparison with the frequent occurrence of secondary neoplasms of that organ, which are found in about 25 per cent of autopsies. Distant metastases of new-growths primary in the liver are potentially common because of the characteristic tendency of the cells to invade the walls and lumina of the venous radicals. Of these metastases, one of the most unusual is that to the skeletal system, a search of the literature revealing only the following nine instances.

Schmidt,¹ in a man of 55, found a primary tumor in the right lobe of a cirrhotic liver, which had invaded the portal veins, and metastasized to the retro-peritoneal tissues, lungs, bronchial glands, skull, sternum and sacrum. Bile capillaries containing yellow staining pigment were noted among the neoplastic cells in the metastases.

Huguennin's² case occurred in a man of 50 years who was known to have had a nodular liver for five years before death. At autopsy, the liver was cirrhotic and contained numerous reddish and green tumors, the former type showing venous invasion microscopically. Metastases were noted in the clavicle, and the dorsal and lumbar vertebrae.

Blumberg³ found a soft gray-green nodular tumor the size of a fist in the right lobe of the liver of a 64 year old man known to have had both lues and diabetes. Metastases to the first, second, and third dorsal vertebrae were present.

The case reported by Catsaras⁴ occurred in a man 65 years of age. A neoplasm in a previously cirrhotic liver had invaded the portal veins into their finest ramifications. Metastases to the neck of the femur caused a pathologic fracture. Bile production in the metastatic tumor cells was noted.

Moon's⁵ case, in a 45 year male negro, also had a pathologic fracture of the right femur. A cirrhotic liver was studded with soft green nodules. Venous invasion by tumor tissue, as well as bile in the metastases, were found microscopically. Other metastases were bilaterally peribronchial.

Geschickter and Copeland⁶ record a case of primary liver neoplasm in a 70 year old male negro, with metastases to pelvis, femur and spine.

Prym⁷ found neoplastic liver cells in a biopsy specimen from a calvarium mass. Bile production and fat infiltration were present. Though no autopsy was done, a large nodular liver was palpable through a relaxed abdominal wall.

Kaufmann⁸ described a case in a man of 33 years who had a tumor in the right lobe of a non-cirrhotic liver, with metastases to pelvic bones, ribs, vertebral bodies, lungs, and abdominal lymph nodes.

Karajanopoulos⁹ found in a man 54 years of age, a tumor in the right lobe of a previously cirrhotic liver, which had metastasized to the manubrium sterni, thoracic vertebrae, and abdominal lymph nodes.

* Received for publication August 19, 1936.

From the Department of Pathology, Beth-El Hospital, Brooklyn, and the Office of the Chief Medical Examiner of the City of New York.

CASE REPORT

A white woman, 29 years of age, was admitted to the orthopedic service of Dr B Koven, at the Beth-El Hospital, Jan 25, 1933, complaining of pain in her left thigh of three months' duration, intermittent but gradually increasing in severity. Terrific pain had confined her to bed for four days before admission.

Her family and past personal histories were negative. No gastrointestinal or urinary symptoms were noted.

The essential findings on physical examination were a shortening of the left lower extremity, outward bowing in the upper third of the corresponding thigh, with crepitation and tenderness at that point. A soft mass the size of a tangerine, adherent to the underlying bony structure, was felt over the eleventh rib below the left scapular angle. No abdominal masses were palpable.

On examination of the blood the hemoglobin estimation was 80 per cent (Sahli), the red blood cells numbered 4,200,000, the white blood cells 7,400 per cu mm with 76 per cent polymorphonuclear neutrophils. The urinary findings, including the examination for Bence-Jones protein, were negative. The blood Wassermann reaction was negative. Nothing unusual was found in the blood chemistry examinations.

Roentgenographic examination demonstrated a pathologic fracture through a neoplastic involvement in the upper third of the left femur, and a similar involvement of the left eleventh rib.

Biopsy of the thoracic mass was done, but the patient died suddenly before a microscopic examination could be made.

Necropsy was performed two hours after death. The body was noted as that of a well developed, fairly well nourished, white woman, about 120 lbs in weight. The left lower extremity was one and a half inches shorter than the right, with abnormal mobility and crepitation at the junction of the upper and middle thirds. A recent 10 cm incision, closed by interrupted cat-gut sutures, through which considerable fluid blood exuded, was present over the eleventh rib in the left scapular line. Nothing found in the head or neck was noteworthy.

Chest The sternum, the right ribs and pleural cavity, and the heart were grossly normal. The left fifth rib 2 cm lateral to the costo-chondral junction was softened in an irregularly circular area 3.2 cm in diameter. The overlying external periosteum and muscular tissue were necrotic, so that slight pressure caused a grumous, dirty, gray-brown material to exude from the rib, the underlying periosteum and parietal pleura were not grossly involved, although expanded a few mm into the pleural cavity. On section the lesion was composed of the grumous material, old blood clot, and a few fine bony spicules. The same rib in the mid-clavicular line presented a fusiform bulge over an area of 2.5 cm caused by an expanding neoplasm in its marrow, similar to the one found in the eleventh rib. The cortex at this point was destroyed and the periosteum moderately thickened. In neither case were the adjacent ribs involved.

The left pleural cavity contained about 200 cc of fluid blood free in the cavity above and below the tumor mass which, displacing periosteum and parietal pleura ahead of it, extended into the pleural cavity from the eleventh rib posteriorly. A small amount of blood was present in several fibrous walled loculi between tumor and lung. Wherever these were separated, the overlying parietal pleura and the periosteum (indistinguishably combined) presented a small, elliptical, smooth edged opening 6 by 3 mm, and several smaller linear openings which led into the tissue composing the tumor mass.

There was a recent operative incision, 10 cm in length, extending parallel to the left eleventh rib posteriorly. To a point 2.5 cm from its vertebral origin, this rib was completely replaced by a fairly soft mass which encroached upon the adjacent ribs. The subcutaneous operative area contained scattered recent hemorrhages and a

layer of cat-gut sutures. Viewed from the pleural surface, the mass was about 7 cm in diameter and projected into the left thorax a distance of 5 cm, displacing thickened parietal pleura before it. There were recent diffuse subpleural hemorrhages over a radius of 10 cm about the tumor. The mass on section was fairly soft, pale green in color, divided into large ovoid lobules by thin fibrous strands. The mass presented several necrotic and occasional faintly outlined hemorrhagic areas.

The eleventh rib was absent in this area, a suggestion of previous periosteum remaining near the still recognizable portion of the rib. The latter had a remarkably thinned cortex, 1 mm in width at the tumor edge, the periosteum raised from its surface by tumor tissue and hemorrhage, and thickened to 1.5 mm. The marrow was soft and brownish and lacked trabecular structure.



FIG 1 Gross photograph of the liver showing the lobulated tumor occupying the greater part of the right lobe. Note the adjacent daughter nodules, the relatively sharp demarcation of tumor from neighboring normal parenchyma, and the absence of cirrhosis in either lobe.

In the three bones in which the marrow and cortex had been invaded by new growth with subsequent pathologic fracture, there was no gross evidence of attempted periosteal or endosteal new bone formation. The periosteum seemed to have been destroyed practically in situ and lifted only to a small degree by the expanding lesion. The adjacent, grossly uninvolved, marrow cavities were neither congested nor softened. After extensive sectioning, the lungs and thoracic lymphatic tissues presented no gross neoplastic involvement.

Abdomen No free fluid or adhesions were present in the peritoneal cavity.

The *liver* measured 24 by 18 by 9 cm and weighed 1400 gm. The outer half of the right lobe was almost completely replaced by a greenish yellow mass, 8.5 cm in diameter, divided by fibrous septa into lobules of an average size of 1.0 to 1.5 cm (figure 1). There were necrotic areas and irregular hemorrhages within these

lobules Adjacent to the larger mass were several similar smaller nodules surrounded by a dark green hepatic parenchyma which was greatly compressed and contained discrete, ovoid, lighter green areas 2 mm in diameter This whole green area was sharply demarcated from the medial half of the right lobe by a narrow fibrous band which puckered the diaphragmatic surface

The remaining hepatic parenchyma was well lobulated and showed no gross changes No cirrhosis was present The portion of Glisson's capsule overlying the tumor was thickened, shreddy, and adherent to the diaphragm The gall-bladder had a thin wall, its mucosa was green, smooth and velvety The biliary ducts were patent throughout and showed no gross alterations of any of their walls The portal and pericholangitic lymph nodes, as well as the retroperitoneal subhepatic tissues were grossly uninvolved The vena cava and portal veins and their larger branches showed no mural or luminal alterations

The *adrenals, kidneys, genitalia* and *pancreas* showed no gross changes

The *gastrointestinal tract* except for mucosal pallor appeared normal There was no enlargement, induration or other change of the mesenteric lymph nodes The thoracic duct and the portal and splanchnic vessels, the vena cava and its tributaries, the aorta and its branches were all grossly normal, including the pelvic vessels and the femoral vessels on both sides to the knee

The *spine* showed no gross changes in the thoracic, lumbar and sacral portions

Extremities There was moderate edema of the left upper anterior thigh The marrow of the left femur from a point 1.5 cm below the midpoint of the junction of the neck and body downward for a distance of 10 cm was completely replaced by rather soft, pale green neoplastic tissue (figure 2) None of the normal trabecular markings remained, the tumor tissue at the edge of recognizable marrow extending into the surrounding soft tissues There was a soft, round, discrete, gray white nodule, 1.2 cm in diameter, 1.8 cm below the upper margin of the greater trochanter and 0.2 cm from its posterior wall The cortex was eroded from within and narrowed, tapering toward the line of a pathologic fracture which extended from a point 7 cm below the upper margin of the greater trochanter downward, forward, and inward, for a distance of 2 cm The tumor tissue here was friable and necrotic, apparently the seat of recent blood extravasation The periosteum was torn through opposite the fracture, and raised by tumor tissue 1.5 cm from the bone on either side There was much hemorrhage into the muscles about the fracture Evidence of healing was absent

The breasts Apart from the occurrence of a small intracanalicular fibroma in the right breast both breasts were normal

Microscopic Examination Liver Throughout the left lobe, and in the right lobe at more than a few centimeters from the mass described above, there are no evident histologic alterations Nearer the mass, the sinusoids become congested so that in a zone of a few millimeters breadth around the mass the picture is one of extreme passive congestion, with red cells present between Kupffer and cord cells, and with the cord cells flattened, frequently separated and showing necrobiotic changes, from granular and vacuolar degeneration to total cyto- and nucleo-rhexis There is in this zone marked distention of bile-capillaries with green granular pigment which gives a positive Gmelin test, and occasionally a positive Turnbull stain In places this pigment outlines the bile capillaries, into the finer intercellular ramifications A few sublobular and larger branches of the hepatic and portal veins are totally filled with tumor thrombi This is observed in the sections taken within 2 cm from the tumor edge, but is not present in sections further removed (figure 3) These thrombi most commonly show either total or partial neoplastic cellular necrobiotic changes, in several places they are permeated by fibrin the tumor cells totally necrotic in the organized and recanalized mass In one section in which all the venous branches are so occluded, two large branches of the hepatic artery are filled with fibrinplatelet

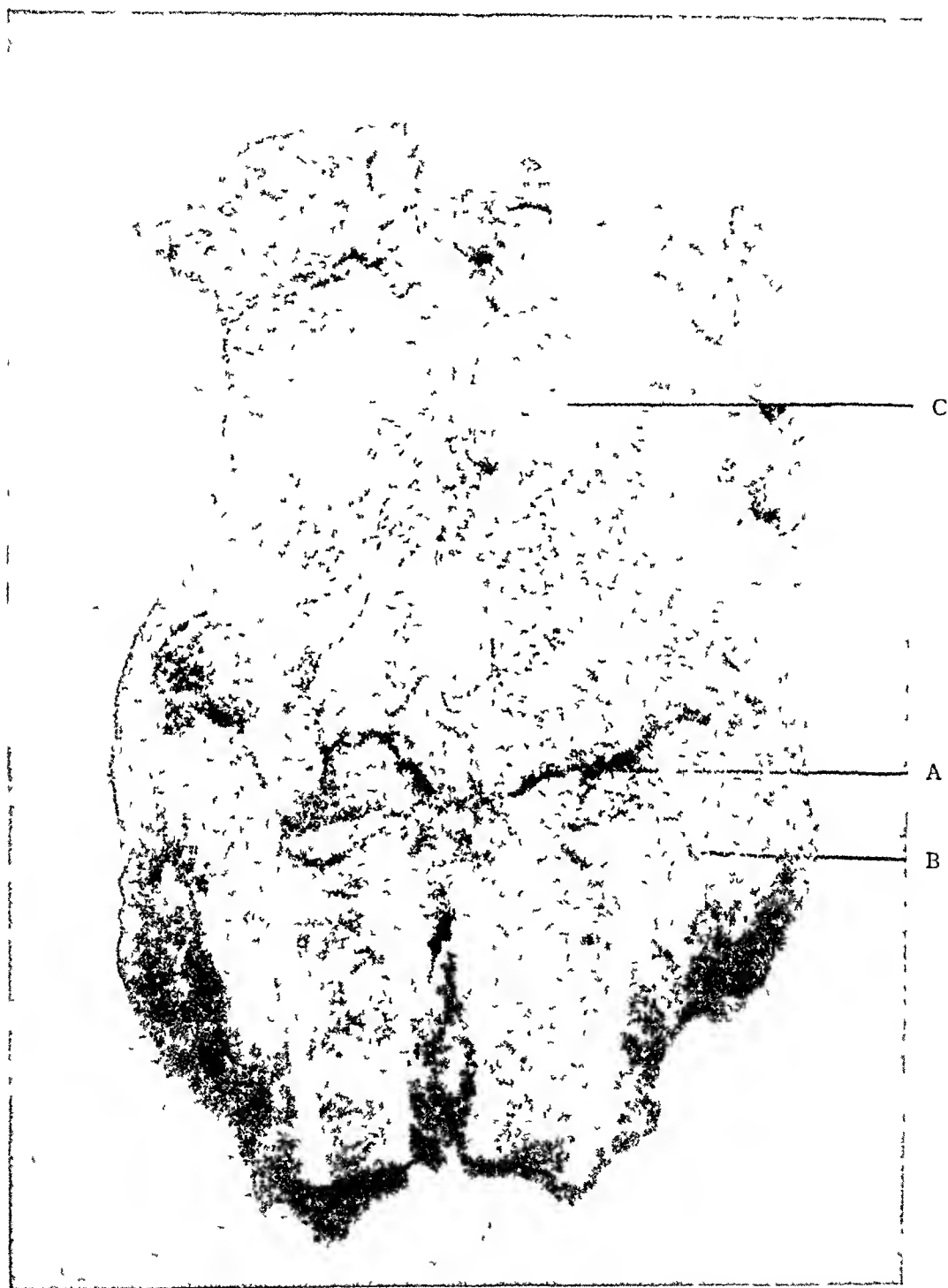


FIG 2 Gross photograph of upper half of left femur showing pathological fracture (A), elevated periosteum and subperiosteal tumor (B), and a solitary nodule in the femoral neck (C)

thrombus, the surrounding hepatic tissue being completely necrotic and heavily infiltrated with partially hemolyzed red cells. The periphery of this sharply outlined area is surrounded by markedly congested normal liver tissue in whose sinusoids are huge numbers of leukocytes. There is no cirrhosis, bile stasis, or cellular infiltration in sections through grossly normal liver except as already noted. Glycogen granules and fat vacuoles (neutral fat) are present regularly and in apparently normal amount in all sections.

The tumor tissue is almost everywhere separated from the surrounding normal tissue by a layer of fibrous tissue, sparsely cellular and poorly vascularized (capillaries), nowhere can any patent transition from the surrounding normal tissue, nor any penetration through the delimiting fibrous tissue be seen, although in places the latter is thinned out almost to single strand thickness. Here and there just beyond the edge of the large mass are small, well circumscribed, round or elongated

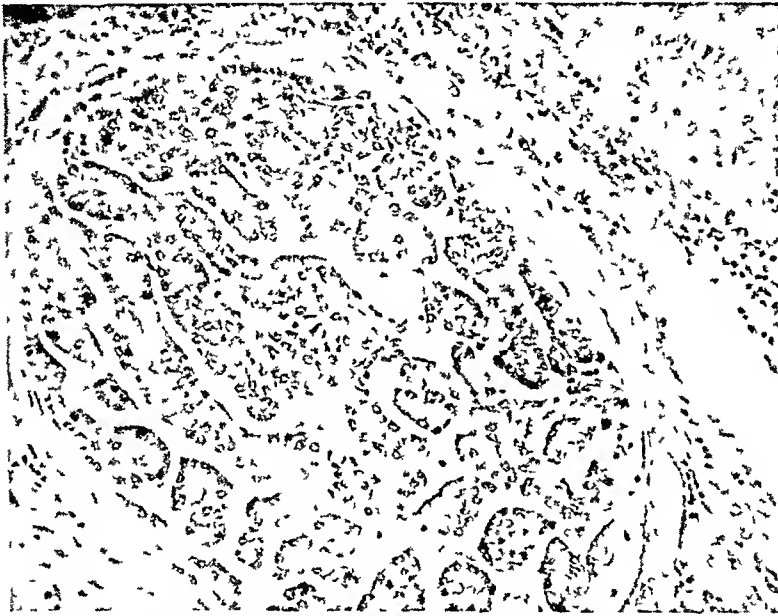


FIG 3 Low power microphotograph of tumor thrombus occluding a sublobular hepatic vein. Note the neighboring inflammatory cellular reaction.

masses of similar cells surrounded by fibrous tissue, lying amid the normal hepatic tissue. In all places, however, where such masses do not totally fill such areas in medullary fashion, the delimiting fibrous tissue is seen centrally to be lined by a single layer of flattened endothelial cells, present throughout the periphery except at points where the cell masses extend into the wall. Erythrocytes are present between the cell masses in such incompletely filled areas. In a few places in the large branches of the hepatic vein around the capsule-like delimiting zone, about the large tumor as well as in some large sinus-like spaces within it, are isolated tumor cells, well preserved and stained, free within the lumen and not enmeshed by fibrin, red or wandering cells. Where larger masses are seen, necrobiotic changes and partial lumen occlusion, to a greater or lesser extent, are the rule.

The tumor itself, as well as the smaller daughter nodules, is composed of masses of cells, arranged chiefly in anastomosing strands two cells in thickness (figure 4). There is a marked tendency to radial arrangement of these strands, particularly in the central portion of the large mass, where an occasional vessel is present in the center

of such a radially arranged zone, these vessels, extremely few in number, are arterial in character. There is nowhere any suggestion of true lobular structure, although dense strands of fibrous tissue carrying capillaries and occasional arterioles penetrate the tumor for varying distances from the delimiting fibrous tissue, with which they are connected.

Between the cells of the individual strands one sees very frequently canaliculi partially or completely filled with finely granular pigment varying from a definite green-yellow to a dirty brownish yellow, giving the Gmelin stain regularly but only very occasionally the Turnbull stain. These capillaries are frequently markedly distended, particularly where the cell masses, cut in cross-section, appear as solid alveoli, and they can be traced as fine ramifications between the individual cord cells. Nowhere can any communication with larger ducts be seen, neither portal canal nor bile duct, nor any pigment phagocytosis is apparent in any section. The cord strands

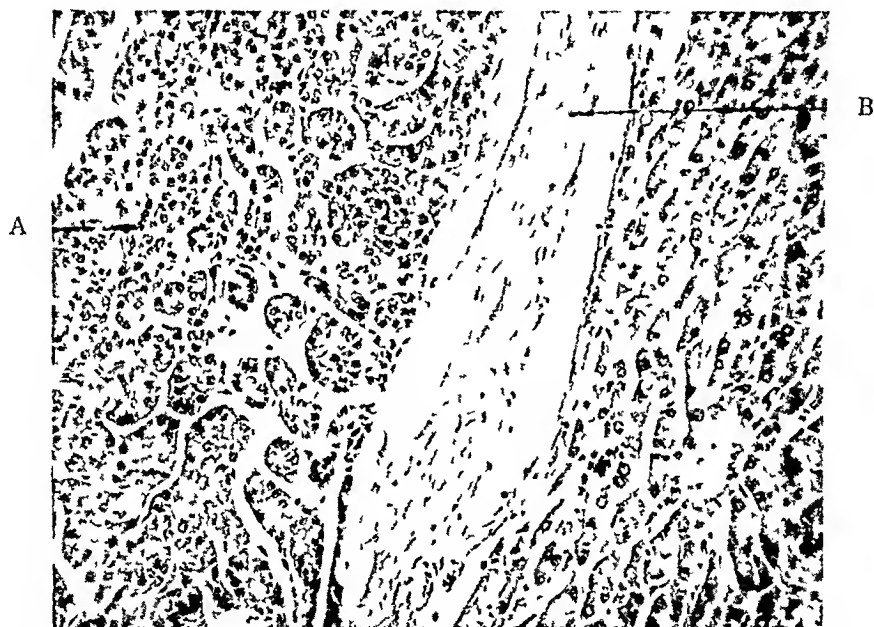


FIG 4 Low power microphotograph of primary hepatic tumor (A) separated from normal liver by poorly vascularized acellular fibrous tissue (B)

are everywhere lined by flattened, stellate-shaped cells resembling in outline and nuclear characteristics Kupffer cells, but being more numerous and having somewhat larger nuclei than is usual in normal cells. In the irregular sinusoidal system between the cords are varying numbers of erythrocytes and scattered leukocytes.

The individual tumor cells are larger than the hepatic cord cells, measuring between 15 to 20 μ . They are well outlined and cuboidal in shape. They have considerable amounts of deeply staining homogeneous acidophilic cytoplasm, and a single round, large, vesicular but hyperchromatic, well-outlined nucleus, with the chromatin peripherally arranged but without well defined nucleolus. Mitoses are extraordinarily rare, there are no amitotic forms, nor do fusion forms or giant cells appear. The cells are remarkably uniform in appearance, except in the smaller intravascular daughter nodules where they are somewhat smaller. Bile canaliculi are absent in such nodules. There is remarkable absence of fatty vacuoles and glycogen granules both in the original growth and its metastases.

The *femur* shows the bone marrow to be replaced entirely by masses of neoplastic

tissue similar to that found in the liver and showing all the elements there described, including bile canaliculi and cord lining cells resembling Kupffer cells (figure 5). The cells are of the smaller variety, in medullary arrangement with small central necrotic areas (figure 6). Only here and there can distinct remnants of marrow

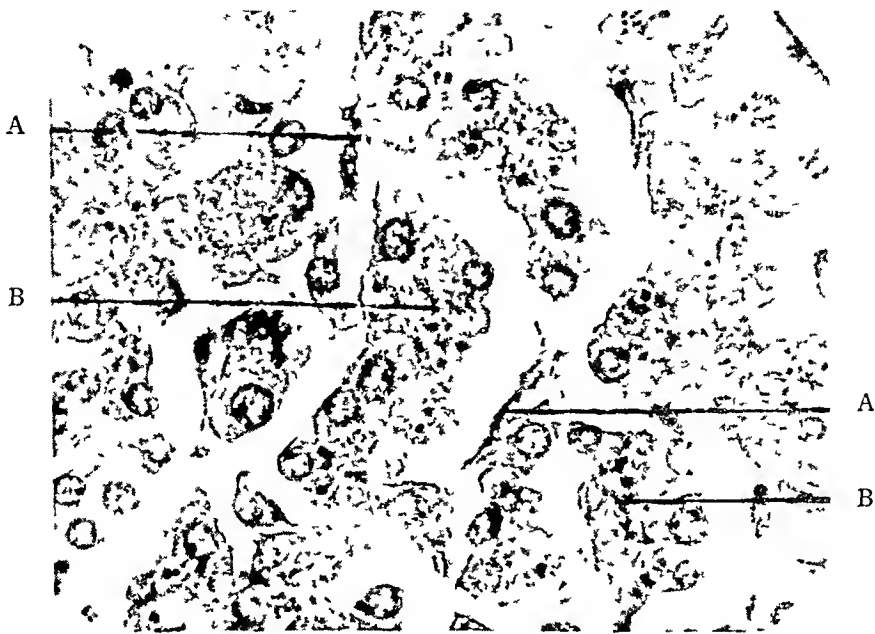


FIG 5 High power microphotograph of femoral metastasis. Note the strand-like two-cell layered arrangement of the neoplastic cells and the elongated Kupffer-like cells (A) separating the cell cords from sinuses. At (B) are two bile capillaries.



FIG 6 Low power microphotograph of femoral metastasis. Note atrophic bone spicule showing decalcified area (A) and lamellae. At (B) is a small vessel resembling a sublobular vein.

reticulum fibers and small patches of erythrocytes, chiefly nucleated, be seen amid the tumor masses. As the line of fracture is approached, the cortical bone trabeculae are narrowed and on their marrow surface show erosions of various sizes, without any apparent osteoclastic hyperplasia, but with a marked and increasing deficiency in lime salts, so that in sections through the fracture itself the trabeculae are totally devoid of such salts, and are separated, with the tumor tissue extending through the line of separation to appear within the periosteum. Likewise toward the fracture from either side, but to a lesser extent than the lime absorptive process, the periosteum is widened, edematous, and very cellular, and the cells fibroblastic in type, at the fracture line, there is a distinct tendency for the cells to be arranged at right angles to the long axis of the bone.

Periosteum and endosteum, indistinguishable in the fracture zone, are infiltrated with moderate numbers of polymorphonuclear leukocytes, elsewhere the lymphocytes predominate in the periosteal infiltrate, while the endosteum is devoid of infiltration. Both the nutrient artery and arterioles in Haversian canals contain tumor cells, but nowhere are there completely plugged vessels.

Sections from areas in the femur not grossly involved, if taken from not more than 3 cm beyond tumor edge, show an occasional tumor nodule or a few cells in vessel and marrow. Active erythropoiesis is apparent.

The ribs show, in all detail, histologic pictures corresponding to those described in the femur. No definite nutrient arterial embolization is demonstrable. Numerous sections of the lungs fail to disclose any tumor tissue within the vessels of whatever order.

This tumor is a primary parenchymal hepatoma, similar in gross appearance to several of those previously reported, though it did not occur in a previously cirrhotic liver. It is the only case with bone metastases reported in a woman, and occurred at 29 years of age, while seven of the nine others were found in patients over 45 years of age. Characteristic extensive vascular invasion and bile production in the metastases were present. As in six of the reported nine cases, evidence of metastases in the lung bed were not found after extensive search. This suggests a specific affinity of the neoplastic cells for the bone marrow in these cases.

The origin of this type of neoplasm is probably in the benign adenoma, whether this be of the congenital type not uncommonly found at the autopsy table or of the type due to proliferation in a parenchyma distorted by cirrhotic changes. That the neoplasm is usually single rather than multicentric in origin is suggested by the frequency with which only a right lobe neoplasm is found (five of the eight cases reported in detail, including our own).

The tumor acts like an organ rather than tissue in its metastases, these present all the structures of the normal liver, including cords of cells in double rows, intervening capillaries, and Kupffer cells. Bile and bile canaliculi are found, the former not undergoing phagocytosis by the Kupffer cells. That the metastasis may have the physiologic activity of the original organ is suggested by the bile formation present in our case. That such functions are not, however, completely the counterpart of the original organ, either in the primary neoplastic focus or the metastases, is suggested by the absence of glycogen granules and fat within the tumors, while the normal liver contained both.

From the standpoint of the clinician, attention should be directed toward the liver in those cases coming under observation with metastatic lesions, espe-

cially those of spine and femur, typically expanding in character and lacking new bone formation, in which the usual primary sites, lung, prostate, thyroid, breast and kidney have been excluded. The liver is likely to escape serious attention because of the tendency of a primary hepatoma to involve one lobe, thereby not interfering with liver function tests, rarely producing jaundice or ascites, and not usually causing appreciable hepatic enlargement or nodulation. Thorotrast injection may aid in outlining such tumors which are most frequently few in number, fairly well demarcated, and sufficiently large to yield shadows if outlined.

SUMMARY

A case of primary liver carcinoma (hepatoma) with bone metastases is reported. Nine cases from the literature are collected and described briefly. Evidence is presented to indicate that this type of neoplasm is organoid rather than histioid, and shows in its metastases morphologic evidence of its original physiologic function. Attention is called to the liver as a focus for metastatic bone neoplasm in obscure cases.

The authors desire to express their thanks to Dr. B. Koven, attending orthopedist at the Beth-El Hospital, for permission to use the clinical data of this case, and to Dr. Thomas A. Gonzales, acting Chief Medical Examiner of the City of New York, for permission to use the pathologic data of this autopsy performed, as assistant medical examiner, by one of us (M. J.).

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ELECTROCARDIOGRAPHIC CHANGES WITH PERFORATED
DUODENAL ULCER, A CASE REPORT¹

By LEMUEL C MCGEE, PH D, M D, HAROLD A CONRAD, M D, and
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C M, male, coal-miner, aged 39 years, entered the hospital one Sunday morning in shock and semi-coma. The history, obtained from his family, was that he had been seized with severe upper-abdominal pain while walking from one room to another in his home 12 hours previously, and that he had collapsed immediately. There had been no radiation of the pain to the sternum. He had become quite short of breath following the onset of pain and could not sleep. The pain had diminished but did not disappear. The next morning, 10 hours after onset of symptoms, a physician was called and the patient received a hypodermic, presumably of morphine. Some time afterward he started on a 50 mile trip, by ambulance, to the hospital.

Just at the time of his arrival, the patient had a recurrence of the excruciating pain in the epigastrium. He exhibited extreme dyspnea, dehydration, cyanosis and a truly rigid abdomen. After saline and glucose had been administered intravenously, the abdomen became pliable and the patient recovered somewhat from shock. An electrocardiogram (figure 1) was taken which presented inversion of T-waves in Leads II and III with elevation of the S-T interval in those leads as well as in Lead IV.

The sudden onset of pain in the epigastrium and the finding of marked rigidity of the muscles of the upper abdomen pointed to acute intra-abdominal disease with peritoneal irritation. The abdominal wall was not rigid for the subsequent few hours and during this time the patient vomited. A tentative diagnosis of either perforated duodenal ulcer or acute pancreatitis was made. When the cardiogram was developed, there arose the possibility of coronary occlusion with posterior surface infarction. The white blood count was 9,900 cells per cu mm. The cervical veins were markedly distended and for a period of two hours there was definite pulmonary edema and a frothy sialorrhea. Heart sounds were faint, with a rate of 140 per minute. The red cell count was 4,740,000 and the blood Kahn was negative. Because of the lapse of more than 12 hours since the onset of the catastrophe and the persisting shock of the patient, the chance offered by surgery was described to the family as being very small. The family wished to have no surgery attempted and this was agreed to by the consulting surgeons and physician.

The patient was removed to a room in the hospital where, unfortunately, electrical interference makes the recording of the electrocardiogram very unsatisfactory, and hence no effort was made to repeat the tracing. A few hours later a third paroxysm of epigastric pain developed and with it, the upper abdomen again became exceedingly rigid for a few hours. The pain at this time extended down in to the left flank. The vomiting continued.

In the periods between throes of severe pain with collapse, the blood pressure rose to 130 systolic and 80 diastolic from a brachial pressure too low to be read immediately after admission. The patient's temperature was, for the most part, between 99° and 100° F rising but once to 100.6° F.

The patient recalled that for the previous six months he had had recurring attacks of rather severe epigastric pain with shortness of breath, and voluntarily stated that his abdominal muscles would become quite "hard" during the attack. The periods of distress were too numerous to count and they appeared only when he was working in the mines or when walking to or from his home. He was positive in

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the assertion that the discomfort was related to exertion, that the pain never extended into the chest or shoulders and that resting a few minutes provided relief. He had never observed that taking of food relieved him but had noticed that the pain was more apt to appear one to three hours after eating than at any other time. There had been no nocturnal distress but he had slept, by preference, on two pillows. For the previous four weeks he had had a cough and had noted faintness and giddiness. He had lost 10 pounds in weight. He drank five or six cups of coffee daily and had had to void urine twice each night. He had stopped work two weeks before because of



FIG 1 Electrocardiogram taken at time of admission. Note low T_2 , inverted T_2 and elevated S-T interval in Leads II and III.

marked dyspnea and weakness. He had been on no medication. In the past he had had a gonorrheal urethritis, a crushed foot, a broken nose, and a broken left arm. He had lost two wives from what had been diagnosed as pulmonary tuberculosis. His father at the age of 75 years, had died after a chronic "gastric" complaint of several years' standing.

The abdomen became quite distended the day following the patient's admission. He received supportive treatment. He died after 70 hours in the hospital. The intriguing history, pointing to myocardial disease, and the terminal illness with death

from evident peritonitis, prompted an autopsy to ascertain whether there were two disease processes present.

The body was that of a man of about 170 pounds, appearing to be older than 39 years. Three liters of a greenish brown fluid were removed from the peritoneal cavity. The peritoneum was generally acutely inflamed. The omentum and superficial coils of bowel were matted with an abundant purulent exudate and thick fibrin. The duodenum was surrounded by both fibrin and firm fibrous adhesions extending to every adjacent structure. The fundus of the gall-bladder covered a perforation in the duodenal wall. The gall-bladder itself was intact but covered with exudate and fibrin. When the duodenum was opened, two typical, chronic "kissing" ulcers were found, the upper one alone having perforated. This ulcer measured about 5 mm by 6 mm in diameter and had thickened margins (figure 2).

The thoracic cavity contained no significant abnormalities. The pericardial sac was normal. The heart weighed 360 grams and the left ventricular wall was 15 mm thick midway between base and apex but otherwise all measurements were well within normal limits. The coronary vessels were healthy in appearance except for a small atheroma in the left coronary about 2 cm from the orifice. Careful dissection of these vessels revealed no occlusion. Extensive sectioning of the myocardium revealed no infarction, either old or recent. There were no other noteworthy findings at the autopsy. The histological study confirmed the interpretation of the gross pathological findings.

An occasional striking association between disease of the gall-bladder and symptoms referable to the heart has been noted in the past 30 years^{1,2}. Carmichael³ noted a bradycardia in a patient having an obstructed cystic duct. The periods of bradycardia were observed three separate times, coinciding with strong contraction of the gall-bladder muscle. Tennant and Zimmerman,⁴ in a statistical study of 1,600 autopsies, found "a significant association between the occurrence of heart disease in general and gall-bladder disease". Fitz-Hugh and Wolferth⁵ reported six patients with cardiac complaints and abnormal electrocardiographic tracings who had gall-stones removed. A few weeks after the operation, the electrocardiographic abnormalities became normal in each patient. Willis and Fitzpatrick⁶ found, in a series of 596 patients, a striking improvement in the cardiovascular condition after treatment for chronic disease of the gall-bladder, even in the group (229 patients) having organic disease of the cardiovascular system. The association between peptic ulcer and cardiac symptoms is undoubtedly less frequently noted. Barker, Wilson and Collier⁷ reported, in 1934, an instance of perforated duodenal ulcer simulating the clinical picture of acute coronary occlusion.

The patient in the present report presented cardiac symptoms prior to the terminal illness. There was no evidence of chronic gall-bladder disease. It is obvious from the history and the finding of scar tissue about the duodenum that the patient had previously had "formes frustes" perforations of one or both the chronic ulcers. In the terminal catastrophe, the fundus of the gall-bladder had been employed to plug the perforation after three distinct leaks of the duodenum with a collapse accompanying each fresh emptying of duodenal contents. The electrocardiographic changes noted may have resulted from, (1) shock and low systemic blood pressure with insufficient oxygenation of the cardiac musculature, (2) embarrassment of circulation due to displacement of the heart by the elevated diaphragm, or (3) a reflex change in cardiac circulation and function initiated by the inflammatory process about the duodenum and gall-bladder.

A common experiment made upon frogs in the physiology laboratory is the production of a bradycardia or even cardiac standstill by light taps on the abdomen. This effect is lost when the vagus nerves are severed. There exists



FIG 2 Photograph showing "kissing" duodenal ulcers. The ulcer on the left had perforated.

ample clinical evidence of the change in cardiac behavior in man initiated by reflexes arising from diseased abdominal viscera. However, it seems to the authors that the physiological changes accompanying shock in this patient were

likely of more import to the heart than reflexes from the acutely inflamed abdominal viscera. Because of the over-emphasis often placed by physicians upon the changes of the electrocardiogram in clinical practice, the findings in this patient are noteworthy. He had no serious heart disease that could be demonstrated after careful anatomic dissection.

Because of the occasional transient, non-specific R-S interval and T-wave changes in a variety of conditions, it is to be regretted that serial tracings were not available.

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EDITORIAL

THE AWARD OF THE JOHN PHILLIPS MEMORIAL MEDAL

THE John Phillips Memorial Medal has been awarded for 1937 to Dr Richard E. Shope, of the Rockefeller Institute for Medical Research, at Princeton, New Jersey. The award is based on Dr Shope's researches with filterable viruses which are regarded as outstanding in medical biology. Among these are (1) the discovery of a tumor of rabbits, which now bears his name, and the demonstration that this tumor, which has many of the characteristics of a malignant neoplasm, is due to a filterable virus, (2) his contributions to the etiology and epidemiology of mad itch in cattle and the establishment of the identity of the virus causing this condition in cattle and that causing pseudorabies in swine, (3) the demonstration that swine influenza is not due to a single agent but is caused by an infection with a filterable virus and a hemophilic bacillus, (4) the production of evidence to focus attention on the possibility that the swine virus has at some time in the past been the agent in human influenza.

THE CHEMOTHERAPY OF HEMOLYTIC STREPTOCOCCUS INFECTIONS

THE report by J. G. Arnold, Jr., in this number of the *ANNALS*, of a case of grave hemolytic streptococcus infection which recovered under treatment with prontosil brings to the attention of our readers a new and promising chemotherapeutic agent.

The report by Domagk¹ in 1935 that the dye "prontosil" exerts a definite protective action in the case of mice infected with virulent hemolytic streptococci aroused widespread interest and stimulated many other workers to investigate the action of this substance. Domagk's findings have been confirmed and extended, particularly by Levaditi and Vaismen,² Colebrook and Kenny,³ Buttle, Gray and Stephenson,⁴ and Long and Bliss.⁵ This preparation is of special interest since, with the exception of optochin in pneumococcus infections, it is the only instance of a drug which exerts a specific action on a bacterial infection.

¹ DOMAGK, G. Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, *Deutsche med. Wchnschr.*, 1935, lxi, 250.

² LEVADITI, C., and VAISMEN, A. Action curative et preventive due chlorhydrate de 4'-sulfamido-2, 4 diamino-azobenzene dans l'infection streptococcique experimentale, *Compt. rend. Acad. d. sc.*, 1935, cc, 1694.

³ COLEBROOK, L., and KENNY, M. Treatment of human puerperal infections, and of experimental infection in mice, with prontosil, *Lancet*, 1936, i, 1297.

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⁵ LONG, P. H., and BLISS, E. A. Para-amino-benzene-sulphonamide and its derivatives, *Jr. Am. Med. Assoc.*, 1937, cxviii, 32.

Prontosil is the hydrochloride of 4-sulfamido 2, 4 diamino-azo-benzene. It is poorly soluble. "Prontosil soluble" is a related substance with a more complicated structural formula which is more soluble and is suitable for parenteral injection. Under the influence of reducing agents these compounds are decomposed *in vitro* into para-amino-benzene-sulphonamide ("prontylin") which is believed to be the active ingredient of these substances. It is thought that a similar reduction is brought about in the body of animals treated with prontosil by the action of the streptococci themselves.

These workers in general agree that after intraperitoneal inoculation with highly virulent strains of beta-hemolytic streptococci, mice suitably treated with any of these substances recover or materially outlive the untreated control animals. Thus in experiments reported by Long and Bliss, untreated control animals receiving from 10 to 100 M.L.D. of culture invariably died on the first or second day, whereas the six treated animals in one series survived from six to 31 days, and in another series all six recovered. These results were obtained even though treatment was begun eight hours after infection and the mice gave positive blood cultures with 100 to 1000 or more colonies per c.c. of blood. Treatment had to be continued for some time or relapse and death occurred. Some difference was noted in the susceptibility of various strains of streptococci to the action of the drug. The results were much less definite when strains of low virulence were used.

The mode of action of the drug is not definitely known. Prontylin (but not prontosil) exerts a moderate bacteriostatic activity when added to cultures of beta-hemolytic streptococci, even in the presence of serum. The serum of animals treated with prontylin also shows an inhibitory effect on the growth of streptococci. No definite bactericidal effect, however, has been noted. Long and Bliss found that in their treated mice films from the peritoneal exudate made 24 to 72 hours after infection showed that active phagocytosis of the streptococci was taking place. At the same time the number of viable organisms in a drop of peritoneal exudate progressively diminished. In untreated mice this was not observed. They believe that the drug injures or affects the organisms in such a way that they become susceptible to phagocytosis. They could not confirm the observations of Levaditi and Vaismen that the drug inhibited the formation of capsules by the organisms. The drug showed relatively little or no protective power against the other species of organisms tested.

Favorable results have also been reported particularly in German and French journals from the use of these drugs in the treatment of human infections. In general these clinical studies were not carefully controlled and are less convincing than the animal experiments. Colebrook and Kenny treated 38 cases of puerperal infection with hemolytic streptococci and reported a mortality of 8 per cent as compared with an average mortality of 22 per cent in cases treated by other methods during the preceding four

years Several patients who recovered had had a severe type of infection in which the prognosis would have been grave Long and Bliss reported favorable results in a series of 19 cases of beta-hemolytic streptococcus infection of various types, including several cases of erysipelas and scarlet fever One patient with otitis media and mastoiditis who recovered had shown a positive blood culture with over 2000 colonies per c c of blood There were two deaths, one nine hours and one 22 hours after treatment was started Both groups of workers were conservative in their claims as to the efficacy of the treatment

Thus far relatively few untoward effects have been reported A transient febrile reaction may follow the parenteral injection of large doses of the drug It is readily absorbed both from the tissues and from the gastrointestinal tract It is excreted quite promptly in the urine, and in cases with impaired renal function the possibility of a dangerous accumulation in the body fluids must be kept in mind Signs of mild renal irritation have been noted in a few cases In three cases Colebrook and Kenny observed cyanosis due to sulphemoglobinemia, but all recovered

This work is still in the experimental stage, and needs to be confirmed The number of patients who have been treated with these drugs is very small, and no series of cases has been adequately controlled The possibility of serious untoward effects has not been excluded It is, therefore, quite impossible to draw any definite conclusions as to the value of this treatment, but the results which have been reported seem sufficiently promising to warrant continued trial under conditions which permit accurate observation, together with adequate controls

P W C

REVIEWS

Principles of Biochemistry By ALBERT P. MATHIJS, Andrew Carnegie Professor of Biochemistry, University of Cincinnati. x+512 pages, 23.5 × 16.5 cm. William Wood and Company, Mt. Royal and Guilford Aves., Baltimore, Maryland. 1936. Price, \$4.50.

Students of the biological sciences have long been acquainted with the author and his familiar and authoritative "Physiological Chemistry," since he has been teaching biochemistry to medical students and contributing to experimental research for forty years. The present volume, however, is shorter and written in a different style—in fact it is an entirely new book. It is written in six parts, namely, Glucides, Lipides and Proteins which constitute the major portion of the book, and Blood and Connective Tissues, Vitamins and Hormones, and Energy Metabolism. The approach to certain subjects, especially the discussion of the carbohydrates, proteins and fats, is somewhat unusual in that the description of their more fundamental chemical principles is smoothly blended with a discussion of the factors influencing their digestion and metabolism, both under normal and pathological conditions. A valuable addition to the subject matter is the discussion of clinical material.

Written in a most interesting manner, the book is very readable and is a good text to use along with the usual set of lectures which are given to medical students. This volume should be especially valuable to the student or young doctor preparing for the board examination, or to doctors or workers in science generally who wish to review and bring up-to-date their knowledge of biochemistry especially as it concerns the human body. The younger student with a flair for research will find its pages a veritable storehouse of enticing problems awaiting solution. The author states that he has omitted "almost all references to the literature as this is not intended to be a reference handbook." This the reviewer feels is to be regretted. The modern medical student is interested in the experimental development of biochemistry, but has had little if any training in consulting the original literature, and certainly receives insufficient assistance along this line while in medical school. It seems unfortunate that Dr. Mathijs, with his great personal knowledge of the historical background of biochemistry, has not made this information available to the student by means of an organized bibliography. This defect, however, is insignificant in comparison with the general excellence of the book.

It was the purpose of the author to "correlate and synthesize the numerous facts, so that they will appear not as an inchoate assembly of facts, but as making part of a great science which reveals the finer structure and coordinated chemistry of the human body." This purpose, in the reviewer's mind, has been well attained.

E. G. S.

Textbook of Surgery By JOHN HOMANS. 4th edition. 1267 pages, 25.5 × 17.5 cm. Charles C. Thomas, Springfield, Illinois, and Baltimore, Maryland. 1936. Price, \$8.00.

Through its four editions since 1931, this book has kept the characteristics intended by its author, namely, an edited reflection of the teaching in the surgical department of the Harvard Medical School developed by Harvey Cushing and his associates. Accordingly it is an almost unique weld of the historical development of surgery, the dogmatism necessary for student teaching and present surgical beliefs.

The present edition differs from the third by the inclusion of chapters on Amputations and Plastic Surgery. This new material is well up to the standard of the remainder of the book.

E. M. H.

The Thyroid—Surgery, Syndromes, Treatment By E P SLOAN, M D 475 pages, 26 × 17.5 cm Published by Charles C Thomas, Springfield, Illinois, and Baltimore, Maryland 1936 Price, \$10.00

This book represents the experience and judgment derived from the observation of 20,000 patients in a thyroid clinic. Although the author states that the book is not intended to be encyclopedic, no phase of his subject has been neglected. The bibliography contains 254 names. The authors of the bibliography are indexed and there are indices of subjects and names. Chapters on the parathyroid glands and the thymus are also included.

In such a monograph there is necessarily much that a reviewer may find to which exception might be taken as to fact or interpretation of fact, but such disagreement in opinion in no way detracts from the value of this book. One might point out that recent work on the lymphatics of the thyroid could have been discussed with advantage in particular connection with some of the author's own ideas. Considerable emphasis is given to an unknown substance which for the purpose of discussion the author calls "thyrom," pictured as the active principle contained in the thyroxin molecule which differentiates thyroxin from iodine. The discussions of the underlying basis of symptoms is interesting. The chapters on surgical treatment are particularly complete with a well presented exposition of the surgical anatomy. In such a well finished production this reviewer regrets to see the use of such a hybrid as "subnormalcy" which the author uses in place of more acceptable wording.

This book will be found a valuable addition to the literature on thyroid disease.

E M H

Modern Treatment of Diseases of the Respiratory System By A LISLE PUNCH, M B, M R C P, and F A KNOTT, M D, M R C P, D P H 295 pages, 14 × 20 cm, illustrated P Blakiston's Son and Co, Inc, Philadelphia 1936

The authors as stated in the preface, have intended this book primarily for the general practitioner and the medical student who is just beginning his hospital training.

From this standpoint they have achieved their purpose admirably. The text is concise and yet comprises an adequate survey of the field of pulmonary disease. The authors have included painstaking descriptions of various clinical procedures, such as the technic of thoracentesis, pneumothorax, etc., and have included illustrations and descriptions of apparatus. The roentgenographic plates are exceedingly good and abundant, and the pathology is clearly pointed out, thus adding materially to the value of the book.

H V L

The Diagnosis and Treatment of Diseases of the Peripheral Arteries By SAUL S SAMUELS, A M, M D 260 pages, 51 illustrations, 22.25 × 15 cm Indexed Oxford University Press, New York 1936 Price, \$3.50

This volume is not an exhaustive treatise on the subject matter of the title. A classification of diseases of the peripheral arteries is presented and methods of examination and diagnosis are described. Thromboangitis obliterans is discussed at some length. The author considers the use of tobacco, especially cigarette smoking, to be a very important factor in the progress of the disease. He emphasizes his belief in the efficacy of intravenous hypertonic saline injections plus rest and postural exercises in the treatment of this condition, and finds most other methods that have been advocated to be of doubtful use or even harmful. There is very little discussion of the other methods of treatment. There is a briefer discussion of arteriosclerosis obliterans and diabetic gangrene. Very short chapters on Raynaud's disease, erythro-

melalgia and essential thrombophilia are included. There is also a chapter on the medico-legal aspects of peripheral arterial disease.

The reviewer does not feel that this book can be recommended as a well balanced discussion of the subject matter of the title. It does forcefully present the author's views on the treatment of thromboangitis obliterans.

W S L

Tuberculosis. By GERALD B WEBB, M D. 205 pages, 17 × 11.5 cm. Paul B Hoeber, Inc., New York. 1936. Price, \$2.00.

Dr Webb's book is the first in the series of Clio Medica limiting itself exclusively to one disease entity and as such sets a noteworthy example for others that will surely follow. In dealing with this age-old disease, so intimately tied up with the history of medicine in general, Dr Webb has divided the subject into its various phases. Practically every chapter takes up just one aspect of the subject of tuberculosis and discusses it in its entirety, chronologically. It is thus possible to get a complete picture of the history of any one phase of the disease by reading the appropriate chapter.

The few illustrations and charts are well chosen and the quotations extremely interesting. It might be worthwhile to translate some of the quotations which are presented in the original. The bibliography and the index of names increase the value of this book. This most recent contribution to the history of tuberculosis will be welcomed by all students of the disease. It is scholarly and informative and yet at the same time readable and entertaining.

M S S

COLLEGE NEWS NOTES

LIFE MEMBER

Dr Samuel A Vogel (Fellow), Buffalo, N Y, has become a Life Member of the College under date of January 25, 1937

GIFTS TO THE COLLEGE LIBRARY

The following gifts to the College Library of publications by members are gratefully acknowledged

Books

- Major Daniel B Faust (Fellow), (MC), U S Army, one autographed book, "Diet Manual, Letterman General Hospital",
Dr Jacob Gutman (Fellow), Brooklyn, N Y—9th Supplement to "New Modern Drugs",
Dr J J Singer (Fellow) and Dr Evarts A Graham, F A C S, St Louis, Mo—one autographed book, "Surgical Diseases of the Chest" (with Harry C Ballou)

Reprints

- Dr Miles J Breuer (Fellow), Lincoln, Nebr—1 reprint,
Dr E H Drake (Fellow), Portland, Maine—3 reprints,
Lt Col Frederick H Foucar (Fellow), (MC), U S Army—1 reprint,
Dr Salvatore Lojacono (Fellow), Tucson, Ariz—1 reprint,
Dr John H Musser (Fellow), New Orleans, La—27 reprints,
Dr E Sterling Nichol (Fellow), Miami, Fla—7 reprints,
Dr William H Ordway (Fellow), Mount McGregor, N Y—3 reprints,
Dr Carleton B Peirce (Fellow), Ann Arbor, Mich—13 reprints,
Dr Horace K Richardson (Fellow), Stockbridge, Mass—3 reprints,
Dr J J Singer (Fellow), St Louis, Mo—20 reprints,
Dr Willard J Davies (Associate), Rockville Centre, N Y—2 reprints,
Dr Everett C Fox (Associate), Dallas, Tex—12 reprints,
Dr Louis L Perkel (Associate), Jersey City, N J—1 reprint
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KENTUCKY MEMBERS HELD ANNUAL MEETING

The Kentucky Fellows and Associates of the American College of Physicians held their annual meeting at Lexington, Ky, January 9, 1937 Dr Ernest B Bradley (Fellow), Lexington, President of the College, Dr C W Dowden (Fellow), Louisville, College Governor for Kentucky, and Dr J W Scott (Fellow), Lexington, Chairman for Arrangements, sponsored the meeting Thirty-five members of the College were in attendance, in spite of extremely inclement weather The afternoon program was as follows

- Dr R W Sparkman (by invitation) "Quantitative Estimations of Glycosuria Following Intravenous Administration of Glucose",
Dr R B Warfield (by invitation) "Calcinosis Universalis",
Dr Ernest B Bradley (Fellow) "An Unusual Type of Lymphosarcoma",
Dr John Harvey (Fellow) "Contracted Kidneys Due to Pyelonephritis",
Dr C H Fortune (Fellow) "Edema of Obscure Type"

In the evening a dinner was held at the LaFayette Hotel. The entire meeting has been reported as a very successful, beneficial and enjoyable one. The policies and practices of the College are more thoroughly understood by the members at large, members are given a closer contact with one another from the social angles of these local meetings, and interest is inspired in the activities of the College.

Dr Henry W Grote (Associate), Bloomington, Ill, has accepted an appointment as head of the Roentgenological Department of the Brokaw Hospital of Bloomington.

Mr William Albert Widmer, head of the medical sales department of the J B Lippincott Company, publishers, died suddenly early in January. Mr Widmer was known widely in the medical profession, because for many years his face was a familiar one at the book exhibits of the J B Lippincott Company at medical meetings all over the country. In fact, Mr Widmer probably was the dean of medical exhibitors, for he was among the very first to initiate the plan of making conveniently available to doctors for examination books or other medical products by displaying them at the annual gatherings of various medical societies.

Mr Theodore A Phillips, for some years associated with the W B Saunders Company, publishers, has been appointed successor to Mr Widmer, with the J B Lippincott Company.

Dr John H Musser (Fellow), New Orleans, was a guest speaker at a meeting of the San Diego (Calif) Academy of Medicine, December 3.

The Stanford University School of Medicine, San Francisco, presents each winter a series of popular medical lectures, given on alternate Friday evenings. Among contributors to the fifty-fifth series now in progress were the following:

Dr Benjamin W Black (Fellow), Oakland, January 22, "The County Hospital and the Public",

Dr William C Voorsanger (Fellow), San Francisco, February 5, "Recent Advances in the Treatment of Tuberculosis".

Dr Samuel A Levine (Fellow), Boston, discussed "Pitfalls in the Diagnosis of Heart Disease" before a joint meeting of the Medical Society of the District of Columbia and the Washington Heart Association on December 9.

Dr John W Ferree (Associate), Bluffton, Ind, has been appointed chief of the recently created bureau of local health administration, Indiana State Division of Public Health.

Dr Donald Gregg (Fellow), Wellesley, Mass, is President of the Massachusetts Society for Mental Hygiene.

On December 16, 1936 a meeting of the Rhode Island Fellows and Associates of the College was held at the John M Peters House of the Rhode Island Hospital. At the meeting, Dr Charles F Gormly was elected Chairman, and Dr Cecil Dustin, Secretary. Dr Guy W Wells was elected Chairman of a program committee of

four members Dr Wells, Dr Alex M Burgess, Governor of the College for Rhode Island, and the Chairman and Secretary of the Rhode Island group, ex-officio Dr Jacob Fine of the Beth Israel Hospital of Boston was the guest speaker of the occasion and gave an interesting account of experimental work on the effect, upon the absorption of gases in the body, of inhalation of concentrated oxygen mixtures

Dr Henry A Christian (Fellow), Hersey Professor of the Theory and Practice of Physics at Harvard University Medical School will prepare and edit future revisions of Osler and McCrae's "The Principles and Practice of Medicine"

Dr N Thomas Saxl (Fellow), New York City, has been appointed Medical Director of the Police Athletic League, an organization formed by the Juvenile Aid Bureau of New York City, for the purpose of providing suitable physical and recreational activities for children with delinquent tendencies

Dr Henry Snure (Fellow) and Dr George Maner presented a paper on "Roentgen-Ray Evidence of Metastatic Malignancy in Bone" before the Radiological Society of North America, on November 30, at Cincinnati, Ohio Their exhibit illustrating their paper won first award in the scientific exhibits

NEW LIFE MEMBERS

The following have become Life Members of the American College of Physicians on the dates indicated

Dr Manfred Kraemer, Newark, N J	January 9, 1937
Dr James W Hunter, Jr, Norfolk, Va	January 9, 1937
Dr Herbert B Smith, Corning, N Y	January 11, 1937
Dr Fresenius Van Nuys, Weston, Mass	January 12, 1937
Dr George M Settle, Baltimore, Md	January 12, 1937
Dr Edward B Vedder, Washington, D C	January 13, 1937
Dr Robert A Peers, Colfax, Calif	January 16, 1937
Dr Joseph Condit, Pasadena, Calif	January 18, 1937
Dr Charles W Stone, Cleveland, Ohio	January 18, 1937

CONDENSED MINUTES OF THE BOARD OF REGENTS

PHILADELPHIA, PA

December 13, 1936

The Board of Regents of the American College of Physicians met at its Philadelphia headquarters, 4200 Pine Street, at 10 00 a m, December 13, 1936, with Dr Ernest B Bradley, President, presiding The following were present

Ernest B Bradley, President
 James H Means, President-Elect
 O H Perry Pepper, First Vice President
 David P Barr, Second Vice President
 Walter L Bierring, Third Vice President
 William D Stroud, Treasurer
 William Gerry Morgan, Secretary-General
 Sydney R Miller

George Morris Piersol
 Robert A Cooke
 Jonathan C Meakins
 Hugh J Morgan
 James E Paullin
 James Alex Miller
 Francis M Pottenger
 Maurice C Pincoffs
 Charles H Cocke

and Mr E R Loveland, Executive Secretary, acting as secretary of the meeting. The Executive Secretary read abstracted Minutes of the Detroit meeting of the Board of Regents, which were approved as read. He then read in full the Minutes of the meeting of the Executive Committee held at Philadelphia on June 21, 1936.

Upon motion by Dr James E Paullin, seconded by Dr George Morris Piersol, and regularly carried, it was

Resolved, that the Board of Regents approve of the action of the Executive Committee, and that their Minutes be adopted.

The Executive Secretary then presented the following communications

- (a) A letter from Dr E L Tuohy, Governor for Minnesota, dated June 29, 1936, recommending the election of an additional Governor for the State of Minnesota, this additional Governor to take over the southern part of Minnesota and, perhaps, the State of South Dakota.

Discussion developed the opinion that it should be possible for Dr Tuohy to obtain adequate information about candidates in southern Minnesota through members of the Mayo group in Rochester, and that it would be better to handle the situation in this way for the present time.

Upon motion by Dr James E Paullin, seconded by Dr George Morris Piersol, it was

Resolved, that Dr Tuohy's communication be acknowledged, and the suggestion concerning handling the Minnesota situation without an additional Governor communicated to him.

- (b) Following advice that the law required the College to have a Certificate of Authority as a Corporation foreign to the State of Pennsylvania to operate its main office in this State, proper steps had been taken to obtain an official Certificate of Authority from the State Department of Pennsylvania.
- (c) Communications from the Social Security Board. Forms had been filled out and returned, with the explanation that the College is a Corporation organized "not for profit." Although no reply or decision had been received from the Social Security Board, the Executive Secretary expressed the opinion that the College would not be subject to the regulations of the Social Security Act.
- (d) A communication from the U S Post Office granting a reclassification of the ANNALS OF INTERNAL MEDICINE, and reducing the mailing rates to 1½¢ per pound, resulting in a considerable saving in the future on postage.

President Bradley then presented a letter, dated July 23, 1936, from Dr George Crile, Chairman of the Board of Regents of the American College of Surgeons. Dr Crile asked whether it would be possible for the American College of Surgeons and the American College of Physicians to jointly consider a plan to eliminate the indiscriminate use of the words "Physician and Surgeon" by men without special training in a special field, and to have each doctor designated in his practice as "Physician," "Surgeon," "Medical Specialist," "Surgical Specialist" or "General

Practitioner" Dr Crile suggested that the General Practitioner should limit his practice to diagnosis, medicine, minor surgery, emergency work and non-operative obstetrics, that the two Colleges should work together to influence the authoritative bodies to bring this change. Dr Bradley had replied, stating that he had no authority to act, but that the matter would be referred to the Board of Regents, who might be disposed to appoint a committee to confer with a committee from the American College of Surgeons. A further communication from Dr Crile indicated that such a committee had been appointed by his organization.

After general discussion, Dr James Alex Miller moved, and Dr James E Paulin seconded the following resolution, which was carried:

Resolved, that the President be authorized to appoint a committee of from one to three members to confer with a similar committee of the American College of Surgeons in any matters in which both bodies may be interested.

Dr William Gerry Morgan, Secretary-General, reported the following deaths since the last meeting of the Board of Regents:

Master

Anders, James M	Philadelphia, Pa	August 29, 1936
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Fellows

Ackerman, James F	Asbury Park, N J	August 5, 1936
Atwell, Jacob C	Butler, Pa	November 2, 1936
Brooks, Harlow	New York, N Y	April 13, 1936
Brundage, Albert H	Woodhaven, N Y	March 12, 1936
Chase, Arthur B	Oklahoma City, Okla	July 20, 1936
Dearman, William A	Whitfield, Miss	November 4, 1936
DeLaney, Matthew A	Carlisle, Pa	November 1, 1936
Gordon, Thomas D	Grand Rapids, Mich	November 20, 1936
Haines, Charles J	Hallstead, Pa	November 3, 1936
Hastings, Gordon Lee	Little Rock, Ark	September 14, 1936
Hinton, Charles C	Macon, Ga	February 25, 1936
Holmes, Arthur D	Detroit, Mich	February 20, 1936
Johnson, Gertrude M	Battle Creek, Mich	January 29, 1936
Klotz, Oskar	Toronto, Ont, Canada	November 3, 1936
Manges, Willis F	Philadelphia, Pa	November 24, 1936
Marchbanks, Howard E	Pittsburg, Kan	August 7, 1936
Marriott, W McKim	San Francisco, Calif	November 11, 1936
Mayer, William H	Pittsburgh, Pa	August 23, 1936
Murray, Peter	New York, N Y	March 6, 1936
Pierce, Alano E	Minot, N D	March 14, 1936
Quintard, Edward	New York, N Y	February 12, 1936
Reyher, Christopher M	Gary, Ind	February 12, 1936
Simon, Sidney K	New Orleans, La	August 5, 1936
Simonds, Clarence E	Willimantic, Conn	April 1, 1936
Spear, Robert	East Chicago, Ind	August 23, 1936
Stern, Arthur	Elizabeth, N J	November 28, 1936
Stoll, Henry F	Hartford, Conn	September 28, 1936
Synnott, Martin J	Montclair, N J	July 15, 1936
Thompson, Edward G	Memphis, Tenn	June 21, 1936
Williams, Alden H	Grand Rapids, Mich	June 10, 1936
Wilson, John D	Scranton, Pa	June 20, 1936

Associates

Moll, Carl F	Flint, Mich	May 1, 1936
Quigley, William J	Cleveland, Ohio	March 8, 1936
Smith, Webster S	Dayton, Ohio	January 30, 1936

President Bradley stated that he would appoint a committee later on to draw up suitable memorials for those who had been past presidents or governors of the College

The following memorial prepared by Dr S Marx White was read by the Secretary-General, Dr Morgan, and a resolution adopted providing that it be spread upon the Minutes of the Board of Regents and a copy sent to Dr Brown's widow

GEORGE E BROWN

"Dr George Elgie Brown was born at Grand Rapids, Michigan, July 16, 1885. He received the degree of M D in 1909 from the University of Michigan, following which he served two years' internship at the Northern Pacific Hospital, Brainerd, Minnesota. He was married to Irma Parker, July 12, 1911. During the years of his practice in internal medicine at Miles City, Montana, from 1911 to 1921, he carried on special studies at Harvard University for five months in 1914, studied organic chemistry in the summer of 1916 at Johns Hopkins University, Baltimore, and was with the Rockefeller Foundation in France in 1918 and 1919. He was appointed first assistant in medicine at the Mayo Clinic, Rochester, Minnesota, February 1, 1921, and made an associate in medicine, April 1, 1922, later becoming head of a section in medicine at the Mayo Clinic, and associate professor of medicine, in the Mayo Foundation, University of Minnesota. He filled these appointments with distinction until his death. Fellow of the American Medical Association and of the American College of Physicians, he was a member of the Board of Regents of the College from 1927 to 1933. He was also a member of the American Society of Clinical Investigation, the Central Society for Clinical Research, the Alumni Association of the Mayo Foundation, the Association of American Physicians, the Central Inter-urban Clinical Club, the Minnesota Society of Internal Medicine and the Southern Minnesota Medical Association. He was a member of Phi Rho Sigma fraternity and of Sigma XI honorary fraternity.

"During the two years' internship in Brainerd and the ten years of practice in Miles City, he exhibited unusual initiative and industry in clinical research. His first paper, entitled 'The Practical Use of Tuberculin in Diagnosis,' was published in 1911 as a result of work done during his internship. Ten more papers, the majority of them in first-class journals, were published during the ten years of active practice in Montana. During these latter years also he was known to have exhibited much ingenuity in the construction of x-ray apparatus for his own use in practice. During the period of nearly fifteen years of association with the Mayo Clinic, the contributions to medical literature bearing his name or as co-author number 115. His contributions revealed marked originality and by them he became one of the leading authorities in this country, particularly in diseases of the vascular system and in arterial hypertension. His standard cold-pressor test for measuring variability in blood pressure, published with E A Hines, Jr, and his contributions with several members of the Mayo Clinic staff have served to break new paths in the ready recognition of hyper-reactors in essential hypertension and in the surgical treatment of certain of the later stages of the disorder. The 200-page monograph on thrombo-angitis obliterans bearing his name is of great practical value in that it serves to show that correct diagnoses can be made without special methods in more than 95 per cent of the cases of the vascular diseases affecting the extremities. His initiative and drive, his helpful, cheerful friendliness and practical, wise counsel will be greatly missed not only in the organizations to which he gave the best years of his life, but also by an almost unlimited number of friends and by the American College of Physicians.

—S MARX WHITE, M D, F A C P"

The Secretary-General then reported the following additional Life Members since the last meeting

Carl Herman Gellenthien, Valmoia, N M
Herman O Mosenthal, New York, N Y
Oiville H Brown, Phoenix, Ariz
Roy L Leak, Middletown, Conn

making a total of sixty-four Life Members

Dr James E Paullin, Chairman of the Committee on Public Relations, reported that his committee had examined into the correspondence and circumstances of the following resignations, which, by resolution of the Board of Regents, were accepted

Fellows

Dr Arthur F Cooper, Memphis, Tenn
Dr William J Young, Louisville, Ky

Associates

Colonel Glenn I Jones (Retired), M C, U S Army
Dr Ernest L Kiesel, Scranton, Pa

The Committee had received a communication from the late Dr James M Anderson (Master) concerning the establishment of a National Health Day. Since this topic of health education is already so well covered by local, state and public health organizations, the Committee merely recommended cooperation with these groups.

The Committee felt that an appeal from the American Association for China Famine and Flood Relief was without the purposes of the College, and recommended no action.

The Committee recommended that the facilities of the American College of Physicians be placed at the disposal of the Council on Medical Education of the American Medical Association for the promotion of residencies in internal medicine in approved hospitals, and that the College express itself as being in sympathy with attempts to develop better training in the field of internal medicine and its related specialties.

On motion by Dr O H Perry Pepper, seconded by Dr William D Stroud, and regularly carried, it was

Resolved, that the recommendations by the Committee on Public Relations be approved.

Reporting as a committee of one, Dr James H Means submitted the following suggested revision of the Fellowship Pledge, in accordance with a resolution adopted by the Board of Regents at one of its Detroit meetings

"Appreciating that the American College of Physicians has been created to foster the noblest principles and traditions of our calling, and having voluntarily accepted membership therein, I solemnly pledge that I will live in conformity with its ideals and regulations to the best of my ability.

"Especially do I dedicate myself to practice medicine following the Golden Rule and the good precepts of the Oath of Hippocrates, to place ever before my own, the welfare of patients dependent upon my professional knowledge and skill, to respect the interest and character of my colleagues, to supplement, as occasion requires, my own judgment with the wisdom and council of competent medical specialists, to render assistance willingly to my colleagues, to extend freely my professional aid to the unfortunate, the poor and the needy, to seek constant increase in medical knowledge through reading of authoritative literature and by attendance at important gatherings of my professional brethren, by study with physicians of eminence, and by free exchange of experience and opinion with my colleagues

"Further, I promise to refrain from seeking the public eye for purposes of self-advancement, to avoid commercialism in all my professional activities, to adjust my fees to the circumstances of my patients and to make them commensurate with the services I have rendered

"Moreover, I hereby condemn and promise to avoid all abasing money trades with brother practitioners or consultants, and I hereby swear that I will strive constantly to spread among all physicians with whom I come in contact a high ethic of practice like that set forth in the Constitution and By-Laws of the American College of Physicians"

Upon motion by Dr Means, seconded by Dr Barr, and regularly carried, it was *Resolved*, that the above Fellowship Pledge be approved in the place of the one heretofore used

Dr Maurice C Pincofs, as Editor of the ANNALS OF INTERNAL MEDICINE, presented a brief report upon the editorial work on the journal

Dr O H Perry Pepper, as Chairman of the House Committee of the College, reported that the new headquarters had been purchased for \$52,500, and after paying incidental expenses in connection with the transfer of title, settlement, etc, the Committee had a balance remaining of \$2,142.75 of the original appropriation for the purchase of the property at 4200 Pine Street, Philadelphia. Of the \$10,000.00 appropriated for alterations and furnishings, \$4,500 approximately had been spent on alterations, and \$4,500 approximately on furnishings, leaving a balance of \$929.16. There had been certain expenditures for taxes, additional insurance, etc, which had been charged against this appropriation, but which Dr Pepper felt should be charged to some other account, as a matter of bookkeeping. He described the alterations and furnishings that had been completed, and the proposed plan for future operation. In appreciation to Mr Charles J Eisenlohr, from whom the property was purchased, Dr Pepper moved the adoption of the following resolution, which was regularly seconded and unanimously carried

Resolved, that the Officers and Regents of the American College of Physicians extend to Mr Charles J Eisenlohr the thanks of the College for his many courtesies incident to the purchase from him of the new College Headquarters and also for his generous gift of various beautiful furnishings, including andirons, draperies, safe cabinet, billiard table, and other valuable items

Dr Sydney R Miller, Chairman of the Committee on Credentials, reported that of 91 names presented for Fellowship, either by promotion from Associateship or directly, 80 were recommended for election, 5 were recommended for election first as Associates, 3 were rejected, and 3 were deferred for further investigation. 186 names had been presented for Associateship, of which 152 were recommended for election, 21 were rejected, and 13 deferred. The names of those recommended for election, both to Fellowship and Associateship, were inspected by the Regents

Upon motion by Dr George Morris Piersol, seconded by Dr James E Paullin, and regularly carried, it was

Resolved, that the following list of 55 be and herewith are elected to Fellowship in the American College of Physicians as of this date, December 13, 1936

Candidates

Sponsors

CALIFORNIA

Morris Henry Nathanson, Los Angeles
(formerly of Minnesota)

Henry L Ulrich, S Marx White, J B Carey,
E L Tuohy

CONNECTICUT

Marcus Backer, Bridgeport

Daniel P Griffin, Charles H Sprague, Henry F
Stoll (deceased)

Henry Caplan, Meriden

Thomas P Murdock, William E Hall, George
Blumer

*Candidates**Sponsors*

MEDICAL CORPS, U S NAVY

Robert Edwin Duncan, Washington, D C	Lyle J Roberts, Robert G Davis, P S Rossiter
Jesse Bundren Helm, Newport, R I	W W Hall, Paul F Dickens, P S Rossiter
Daniel Hunt, Annapolis, Md	Louis H Roddis, S S Cook, P S Rossiter
Howard Howlett Montgomery, Washington, D C	O J Mink (deceased), C R Baker, P S Rossiter
Lloyd Russell Newhouser, Annapolis, Md	C R Baker, Louis H Roddis, P S Rossiter
Harold Eugene Ragle, Washington, D C	Lyle J Roberts, Paul F Dickens, P S Rossiter
Clarence Wesley Ross, Washington, D C	Louis H Roddis, E R Stitt, P S Rossiter
Robert Franklin Sledge, Washington, D C	Paul F Dickens, W W Hall, P S Rossiter
William Henry Hart Turville, Portsmouth, Va	C R Baker, G E Thomas, P S Rossiter
Paul White Wilson, Washington, D C	E R Stitt, Lyle J Roberts, P S Rossiter

U S PUBLIC HEALTH SERVICE

Thomas Parran, Washington, D C	Thomas A Groover, Oscar B Hunter, Wallace M Yater
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FLORIDA

Warren Wilson Quillian, Coral Gables	P B Welch, George L Cook, T Z Cason
Mathew Jay Flipse, Miami	P B Welch, Kenneth Phillips, T Z Cason
E Sterling Nichol, Miami	P B Welch, Kenneth Phillips, T Z Cason

GEORGIA

Jack Clayton Norris, Atlanta	John B Fitts, H C Sauls, Glenville Giddings
Roy Rachford Kracke, Emory University	Joseph Yampolsky, Trimble Johnson, Glenville Giddings
Samuel Frederick Rosen, Savannah	J Reid Broderick, Lee Howard, Glenville Giddings

ILLINOIS

Grant Harrison Laing, Chicago	Joseph L Miller, George H Coleman, Arthur R Elliott, James G Carr
Lowell Delford Snorf, Chicago	Charles A Elliott, Arthur E Mahle, James G Carr

IOWA

Frederick William Mulsow, Cedar Rapids	Jeannette Dean-Throckmorton, John H Peck, Fred M Smith
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MASSACHUSETTS

Erwin Hartwell Taylor, Pittsfield	William Henry Watters, Sara M Jordan, William B Breed
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MICHIGAN

Charles Vernon Crane, Grand Rapids	Abel J Baker, Burton R Corbus, Henry R Carstens
George Courtney Stucky, Lansing	L G Christian, Milton Shaw, Henry R Carstens

MINNESOTA

Ragnvald S Ylvisaker, Minneapolis	Edwin L Gardner, Archie H Beard, E L Tuohy
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*Candidates**Sponsors*

MISSOURI

Paul Forrey Stookey, Kansas City
Anthony Bigelow Day, St Louis

D D Stofer, Harry L Jones, A C Griffith
Walter Baumgarten, Howard A Rusk, A C Griffith

Llewellyn Sale, St Louis

Harry L Alexander, Ralph Kinsella, David P Barr,
A C Griffith

MONTANA

John Paul Ritchey, Missoula

Allen R Foss, Wybren Hiemstra, Louis H Flugman

NEBRASKA

Frederick Wilhelm Niehaus, Omaha

Rodney W Bliss, Lynn T Hall, Adolph Sachs

NEW JERSEY

Joseph Wiener, Asbury Park
Henry Charles Crossfield, East Orange

W G Herrman, C A Pons, Clarence L Andrews
Walter G Lough, A Wilbur Duryee, Robert A
Cooke, Clarence L Andrews

NEW YORK

Roy Lorraine Scott, Buffalo
William Herbert Ordway, Mount Mc-
Gregor
Benjamin I Ashe, New York

Nelson G Russell, Clayton W Greene, Allen A
Jones
Lawrason Brown, J Burns Amberson, Jr, Grant
Thorburn, Allen A Jones, Walter W Palmer
Herman O Mosenthal, Milton A Bridges, Walter
W Palmer

Zacharias Bercovitz, New York

A Wilbur Duryee, Irving S Wright, Walter W
Palmer

Maurice Coleman Harris, New York
Walter Roger Scott, Niagara Falls

Samuel Weiss, Robert Chobot, Robert A Cooke
Edward C Koenig, Clayton W Greene, Allen A
Jones

Edwin Philip Russell, Rome

William S McCann, Lester Betts, David P Barr,
Allen A Jones

Isaac Shapiro, Schenectady

Lester Betts, Frank vander Bogert, Robert A
Cooke

NORTH CAROLINA

John Alexander Shaw, Fayetteville

W T Rainey, P P McCain, C H Cocke

OHIO

Edward Harvey Cushing, Cleveland

J M Hayman, Jr, Charles T Way, William D
Stroud, A B Brower

Edward Winfield Miskall, East Liver-
pool

Fred B Wilson, R R Snowden, E Bosworth
McCready, A B Brower

OKLAHOMA

Cad Walder Arrendell, Ponca City

Carroll M Pounders, Douglas M Gordon Lea A
Riely

OREGON

Leon Albert Goldsmith, Portland

John H Fitzgibbon, Laurence Selling, T Homer
Coffen

PENNSYLVANIA

Laurence Coleman Milstead, Allentown

Henry I Klopp, Francis J Dever, E J G Beard-
sley

*Candidates**Sponsors*

RHODE ISLAND

Clifton Briggs Leech, Providence

Charles F Gormly, Herman A Lawson, Alexander M Burgess

Elihu Smith Wing, Providence

Charles F Gormly, Samuel A Levine, Alexander M Burgess

TEXAS

James Howard Park, Jr, Houston

M L Graves, Alvis E Greer, C T Stone

George Washington Parson, Texarkana

Bayard T Horton, E V Allen, C T Stone

TERRITORY OF HAWAII

Nils Paul Larsen, Honolulu

W W Boardman, Ernest S duBray, James F Churchill

CANADA

New Brunswick

Arthur Brittan Walter, St John

Hugh A Farris, R H M Hardisty, D Sclater Lewis

Ontario

Ross Martin Lymburner, Hamilton

F A Willius, J H Holbrook, Jabez H Elliott

Resolved, that the following list of 24 candidates be and herewith are elected to Fellowship as of April 18, 1937, due to the fact that their three-year minimum Associate period does not expire until that time

*Candidates**Sponsors*

ARIZONA

Redford Alexander Wilson, Tucson

S C Davis, Charles S Kibler, W Warner Watkins

CALIFORNIA

Frederick Samuel Modern, Los Angeles

E Richmond Ware, Roland Cummings, James F Churchill

DISTRICT OF COLUMBIA

William Phillip Argy, Jr, Washington

Matthew White Perry, Paul F Dickens, Wallace M Yater

INDIANA

Horace McMurren Banks, Indianapolis

Larue D Carter, Edgar F Kiser, Robert M Moore

KENTUCKY

John Richard Gott, Jr, Louisville

Hugh R Leavell, John Walker Moore, C W Dowden

Maurice Gray Buckles, Waverly Hills

J Murray Kinsman, Morris Flexner, C W Dowden

LOUISIANA

Edgar Hull, New Orleans

Clyde Brooks, Ben R Heninger, J E Knighton

Carlo Joseph Tripoli, New Orleans

Clyde Brooks, Ben R Heninger, J E Knighton

MASSACHUSETTS

Lyman Howard Hoyt, Boston

Henry A Christian, Elliott P Joslin, William B Breed

Alexander Marble, Boston

F Gorham Brigham, Walter Bauer, William B Breed

<i>Candidates</i>	<i>Sponsors</i>
	MICHIGAN
Carleton Barnhart Peirce, Ann Arbor	Cyrus C Sturgis, Carl V Weller, Henry R Carstens
John Vincent Fopeano, Battle Creek	Margaret Bell, W M Brace, Henry R Carstens
William S Reveno, Detroit	Frederick G Buesser, Richard M McKean, Henry R Carstens
	MINNLSOTA
Oren Leshe Kirklin, Rochester	A R Barnes, Austin C Davis, E L Tuohy
	NLBRASKA
John Marshall Neely, Lincoln	George W Covey, F L Rogers, Adolph Sachs
	NEW YORK
Leonard M Niesen, Livingston	Harry A Pattison, Lawrason Brown, James Alex Miller, Walter W Palmer
	OHIO
Bruce Kenneth Wiseman, Columbus	Charles A Doan, Walter M Simpson, A B Brower
Edward Everett Campbell, Columbus	John Dudley Dunham, E F McCampbell, A B Brower
	PENNSYLVANIA
George Booth, Pittsburgh	Frank A Evans, C C Wholey, E Bosworth McCready
	RHODE ISLAND
Jacob E Greenstein, Providence	John F Kenney, Charles F Gormly, Alex M Burgess
	TENNESSEE
Henry Clay Long, Knoxville	Robert B Wood, E R Zemp, J O Manier
	TEXAS
Samuel Ainslie Shelburne, Dallas	D W Carter, Jr, J Shirley Sweeney, C T Stone
	VIRGINIA
Alfred Brownley Hodges, Norfolk	F C Rinker, Frank H Redwood, J Morrison Hutcheson
	WISCONSIN
Annette Clarke Washburne, Madison	J S Evans, William S Middleton, Rock Sleyster

Resolved, that the following 157 candidates be and herewith are elected to Associateship in the American College of Physicians

ELECTIONS TO ASSOCIATESHIP

<i>Candidates</i>	<i>Sponsors</i>
	ALABAMA
Joe Hollis Little, Mobile	E S Sledge, Daniel T McCall, Fred W Wilkerson
	ARIZONA
Zebud MacKay Flinn, Prescott	Earle Wood Phillips, Frank J Milloy, W Warner Watkins

*Candidates**Sponsors*

ARKANSAS

John Hernian Baird (U S V A), North Little Rock Philip B Matz, Charles M Griffith, Oliver C Melson

CALIFORNIA

Oran Idnre Cutler, Loma Linda Newton Evans, Percy T Magan, James F Churchill
 Donald E Griggs, Los Angeles R Manning Clarke, Percy T Magan, James F Churchill
 Elliott Plummer Smart, Olive View Edward W Hayes, Robert L Cunningham, James F Churchill
 John Carl Schlappi, San Diego William H Barrow, R H Sundberg, James F Churchill
 Albert Howell Elliot, Jr, Santa Barbara Franklin R Nuzum, W D Sansum, James F Churchill
 Richard Donald Evans, Santa Barbara Franklin R Nuzum, W D Sansum, James F Churchill
 Harrie Augustus Patterson (U S V A), West Los Angeles M K Wylder, L S Peters, H S Cumming, Charles M Griffith

COLORADO

Raymond James Savage, Denver W Bernard Yegge, Clough Turrill Burnett, Gerald B Webb
 Alfred Martin Wolfe, Denver W Bernard Yegge, Lorenz W Frank, Gerald B Webb

CONNECTICUT

Lee D van Antwerp, Meriden Thomas P Murdock, Cole B Gibson, George Blumer
 Morris Albert Hankin, New Haven Theodore S Evans, S J Goldberg, George Blumer

DELAWARE

Gerald Aloysius Beatty, Wilmington B M Allen, W H Kraemer, Lewis B Flinn

MEDICAL CORPS, U S NAVY

Irwin Louis Vincent Norman, Chelsea, Mass Louis H Roddis, E V Allen, P S Rossiter

U S PUBLIC HEALTH SERVICE

William Hyatt Gordon, Fort Stanton, N M Carl Mulky, M K Wylder, L S Peters

DISTRICT OF COLUMBIA

James Wallace Esler, Washington Matthew White Perry, W A Bloedorn, Wallace M Yater
 Henry B Gwynn, Washington Thomas S Lee, Matthew White Perry, Wallace M Yater
 Edward Patrick McLarney, Washington Frank Leech, E Clarence Rice, Wallace M Yater

FLORIDA

James Loudon Borland, Jacksonville R H McGinnis, Louie Limbaugh, T Z Cason
 L Sydnor Laffitte, Jacksonville R H McGinnis, Louie Limbaugh, T Z Cason
 J Webster Merritt, Jacksonville R H McGinnis, Louie Limbaugh, T Z Cason

*Candidates**Sponsors*

GEORGIA

Mark Stovall Dougherty, Jr , Atlanta	Joseph Yampolsky, Trimble Johnson, Glenville Giddings
William Hugh Trimble, Atlanta	Joseph Yampolsky, Trimble Johnson, Glenville Giddings
Richard Hugh Wood, Atlanta	John Baker Fitts, H C Sauls, Glenville Giddings
Francis Power Parker, Emory University	Joseph Yampolsky, Trimble Johnson, Glenville Giddings
Thomas Llewellyn Ross, Jr , Macon	Joseph Yampolsky, Trimble Johnson, Glenville Giddings
William P Harbin, Jr , Rome	Joseph Yampolsky, Trimble Johnson, Glenville Giddings
James Clayton Metts, Savannah	J Reid Broderick, Lee Howard, Glenville Giddings

ILLINOIS

M Herbert Barker, Chicago	N S Davis, III, Clifford J Barborka, James G Carr
Faris Franklin Chesley, Chicago	George H Coleman, Arthur R Elliott, James G Carr
Israel Davidsohn, Chicago	Philip B Matz, Oscar B Hunter, James G Carr
Samuel Glenwood Plice, Chicago	Laurence E Hines, David E Markson, James G Carr
Herbert Albert Sacks, Chicago	A A Goldsmith, Charles A Elliott, James G Carr
Emil George Vrtiak, Chicago	Ernest E Irons, Sidney A Portis, James G Carr
Michael Zeller, Chicago	Harold A Rosenbaum, Josiah J Moore, James G Carr
Harry Allen Richter, Evanston	H A McGuigan, N S Davis, III, James G Carr
Richard Hale Young, Evanston	A C Ivy, Arthur E Mahle, James G Carr
Douglas Boyd, Highland Park	David E Markson, N S Davis, III, James G Carr
Harry W Shuman, Rock Island	B J Cronwell, H A Beam, Samuel E Munson

KANSAS

James Abram Butin, Chanute	Howard E Marchbanks (deceased), William C Menninger, Thomas T Holt
George Arthur Westfall, Halstead	P T Bohan, Henry N Tihen, Thomas T Holt
Arthur Joseph Revell, Pittsburg	William C Menninger, Ralph M Fellows, Thomas T Holt
Kenneth Lewis Druet, Salina	Henry N Tihen, Harold W Palmer, Thomas T Holt
John Lewis Kleinheksel, Wichita	Henry N Tihen, E V Allen, Thomas T Holt

KENTUCKY

Edward Cornelius Humphrey, Louisville	J Murray Kinsman, H V Noland, C W Dowden
Archibald Donaldson Kennedy, Louisville	J Murray Kinsman, H V Noland, C W Dowden
Woodford Bates Troutman, Louisville	Sam A Overstreet, John Walker Moore, C W Dowden

LOUISIANA

Stanley George Wolfe, Shreveport	Marion D Hargrove, Clarence H Webb, J E Knighton
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MAINE

Donald Howard Daniels, Portland	E H Drake, Mortimer Warren, E W Gehring
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*Candidates**Sponsors*

Robert W Garis, Baltimore
 Francis Wilcox Gluck, Baltimore
 Charles Franklin Mohr, Baltimore
 David Tenner, Baltimore
 Perry Franklin Prather, Hagerstown

MARYLAND

Thomas P Sprunt, Walter A Baetjer, Henry M Thomas, Jr
 Louis P Hamburger, Walter A Baetjer, Henry M Thomas, Jr
 Walter A Baetjer, Thomas P Sprunt, Henry M Thomas, Jr
 Louis Kruse, John E Legge, M C Pincoffs
 Victor F Cullen, R S Stauffer, Henry M Thomas, Jr

Earle MacArthur Chapman, Boston
 Greene Fitz Hugh, Boston
 James Carlin McAdams, Fall River

MASSACHUSETTS

F Dennette Adams, B H Ragle, William B Breed
 Maurice Fremont-Smith, Albert A Hornor, William B Breed
 William Mason, Charles C Wolferth, J H Means, William B Breed

Herman Marvin Pollard, Ann Arbor
 Henry Barthell Steinbach, Detroit
 Martin Hugh Hoffmann, Eloise
 John Doyle Littig, Kalamazoo
 Leland E Holly, Muskegon
 Edward Kupka, Pontiac
 Richard Ellsworth Olsen, Pontiac

MICHIGAN

Cyrus C Sturgis, Frank N Wilson Henry R Carstens
 Rollin H Stevens, Hugo A Freund, Henry R Carstens
 William J Stapleton, Jr, Henry A Luce, Henry R Carstens
 Cyrus C Sturgis, Arthur C Curtis, Henry R Carstens
 William M LeFevre, Lawrence Reynolds, Henry R Carstens
 William H Gordon, George A Sherman, James D Bruce
 Harold R Roehm, George A Sherman Henry R Carstens

Thomas Williams Baker, Rochester
 Thomas Jan Dry, Rochester
 Grace Arabell Goldsmith, Rochester
 John Harold Mills, Rochester
 Hendrik Marinus Rozendaal, Rochester
 Jan Henrik Tilisch, Rochester

MINNESOTA

F A Willius, E V Allen, E L Tuohy
 F A Willius, E V Allen, E L Tuohy
 E V Allen, Henry W Woltman, E L Tuohy
 Russell M Wilder, E V Allen, E L Tuohy
 H Z Giffin, Charles H Watkins, E L Tuohy
 P S Hench, P G Boman, E L Tuohy

Douglas Davison Baugh, Houston

MISSISSIPPI

Felix J Underwood, J M Bamber, G W F Rembert

Herbert J Rinkel, Kansas City
 Sim F Beam, St Louis
 Kenneth F Glaze, St Louis

MISSOURI

L P Gay, William W Duke, A C Griffith
 Walter Baumgarten, Howard A Rusk, A C Griffith
 Walter Baumgarten, Charles Hugh Neilson, A C Griffith
 Howard A Rusk, Walter Baumgarten, David Barr, A C Griffith
 Howard A Rusk, Walter Baumgarten, David Barr, A C Griffith

Harold Gould Newman, St Louis
 David Miller Skilling, Jr, St Louis

*Candidates**Sponsors*

MONTANA

Ellis K. Giere, Fort Peck
Malcolm Duncan Winter, Miles City

Jay C. Davis, S. Marx White, Louis H. Fligman
Allen R. Foss, Wybren Hiemstra, Louis H. Fligman

NEBRASKA

Karl W. Brimmer, McCook
Augustus David Cloyd, Omaha
Chester Quay Thompson, Omaha

G. L. Pinney, A. F. Tyler, Adolph Sachs
Rodney W. Bliss, Warren Thompson, Adolph Sachs
Rodney W. Bliss, John R. Kleyla, Adolph Sachs

NEW JERSEY

Robert Brannan Durham, Atlantic City

Hilton S. Read, William W. Fox, Clarence L. Andrews

Richard Dabney Anderson, Burlington

Marcus W. Newcomb, Thomas Fitz-Hugh, Jr., Clarence L. Andrews

Jerome George Kaufman, Newark

Aaron E. Parsonnet, Edgar Mayer, Clarence L. Andrews

Benjamin Saslow, Newark

Manfred Kraemer, Charles E. Teeter, Clarence L. Andrews

Sigurd Walter Johnsen, Passaic

Anthony Bassler, Samuel Weiss, Clarence L. Andrews

Louis Francis Albright, Spring Lake

William G. Herrman, C. A. Pons, Clarence L. Andrews

NEW YORK

George W. Weber, Albany

Frederic W. Holcomb, F. H. Voss, Walter W. Palmer

George B. Dorff, Brooklyn

Maurice J. Dattelbaum, Harry R. Litchfield, Walter W. Palmer

Herman Tarnower, Brooklyn

J. Burns Amberson, Jr., Henry H. Haft, Walter W. Palmer

Ramsdell Gurney, Buffalo

Nelson G. Russell, A. H. Aaron, Allen A. Jones

Frank Meyers, Buffalo

A. H. Aaron, Francis D. Leopold, Allen A. Jones

Stuart L. Vaughan, Buffalo

Nelson G. Russell, A. H. Aaron, Allen A. Jones

Alan Ramseur Anderson, Freeport

Irving Sherwood Wright, Arthur Freeborn Chace, Walter W. Palmer

Arthur Julian Horton, Hollis

Carl Boettiger, Charles M. Levin, Goodwin A. Distler, Robert A. Cooke

LeMoyne Copeland Kelly, New York

R. Garfield Snyder, Lewis A. Conner, Walter W. Palmer

Ralph Horton, Oneonta

Max Pinner, J. Burns Amberson, Jr., Robert A. Cooke

Meyer S. Rednick, Ossining

Arthur F. Heyl, Warren F. Kahle, Walter W. Palmer

Preston Hepburn Watters, Rochester

William S. McCann, Charles B. F. Gibbs, Allen A. Jones

George Johnson, Staten Island

Alexis T. Mays, Edward E. Cornwall, Walter W. Palmer

Clement Joseph Handron, Troy

Crawford R. Green, James F. Rooney, Robert A. Cooke

Alson J. Hull, Troy

Crawford R. Green, Harry W. Carey, Robert A. Cooke

*Candidates**Sponsors*

NORTH CAROLINA

Merle Dumont Bonner, Jamestown	D Waldo Holt, P W Flagge, C H Cocke
Erle B Craven, Jr, Lexington	Harold L Amoss, Robert L Felts, C H Cocke
David Edman Quinn (U S V A), Oteen	Philip B Matz, Charles M Griffith, C H Cocke

OHIO

Ian Bruce Hamilton, Canton	Charles A LaMont, Casper H Benson, A B Brower
Louis Nicholas Jentgen, Columbus	Charles A Doan, John Dudley Dunham, A B Brower
Phillip T Knies, Columbus	Charles A Doan, John Dudley Dunham, A B Brower
Myron D Miller, Columbus	Charles A Doan, Casper H Benson, A B Brower

OKLAHOMA

Elbert Henderson Shuller, McAlester	T H McCarley, Henry H Turner, Lea A Riely
Coyne Herbert Campbell, Oklahoma City	Henry H Turner, L J Moorman, Lea A Riely

PENNSYLVANIA

Willard Daniel Kline, Allentown	Henry I Klopp, Francis J Dever, E J G Beardsley
William J Armstrong, Butler	J C Atwell (deceased), I ester Hollander, E Bosworth McCready
John W Shadle, Butler	J C Atwell (deceased), R R Snowden, E Bosworth McCready
Thomas A Johnson Drexel Hill	Thomas Klein, Joseph T Beardwood, Jr, George Morris Piersol
David I Perry, New Castle	Wayne W Bissell, Ehah Kaplan, E Bosworth McCready
Albert Warner Dewey, Philadelphia	Winfred Dana, George C Griffith, George Morris Piersol
Maurice Spencer Jacobs, Philadelphia	David Riesman, Joseph C Doane, E J G Beardsley
John H Willard, Philadelphia	H L Bockus, Russell S Boles, E J G Beardsley
Wilfred Derwood Langley, Sayre	Stanley D Conklin, C H DeWan, E J G Beardsley
Hyman A Slesinger, Windber	Elwood W Stutzel, H B Anderson, E Bosworth McCready

RHODE ISLAND

Francis Hasseltine Chafee, Providence	Guy W Wells, Charles F Gormly, Alexander M Burgess
Frank Bryant Cutts, Providence	Guy W Wells, Charles F Gormly, Alexander M Burgess
Morgan Cutts, Providence	Guy W Wells, Herman A Lawson Alexander M Burgess
Cecil Calvert Dustin, Providence	Guy W Wells, Charles F Gormly, Alexander M Burgess
John Church Ham, Providence	Herman A Lawson, Guy W Wells, Alexander M Burgess

*Candidates**Sponsors*

TENNESSEE

Philip Henry Levinson, Chattanooga	Leopold Shumacker, Franklin B. Bogart, J. O. Manier
Charles Leroy Denton, Dyersburg	Otis S. Warr, William C. Chaney, J. O. Manier
Edward Guy Campbell, Memphis	Otis S. Warr, William C. Chaney, J. O. Manier
William Frazier Dobyns (U. S. V. A.), Memphis	Charles M. Griffith, E. J. Rose
Henry B. Gotten, Memphis	Otis S. Warr, William C. Chaney, J. O. Manier
Joseph Franklin Hamilton, Memphis	Otis S. Warr, Conley H. Sanford, J. O. Manier

TEXAS

Leslie McKnight Smith, El Paso	Orville E. Egbert, C. M. Hendricks, C. T. Stone
John Arthur Alvarez, Houston	F. R. Luminus, George Herrmann, C. T. Stone
William Henry Cade, San Antonio	Lee Rice, Robert M. Barton, C. T. Stone

UTAH

Richard Francis McLaughlin, Price	O. J. LaBarge, L. E. Viko, G. Gill Richards
William C. Walker, Salt Lake City	Otis Wildman, Frederick Ceres, George Morris Piersol

VIRGINIA

John Braxton McKee, Winchester	Dean B. Core, R. Finley Gayle, Jr., J. Morrison Hutcheson
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WASHINGTON

John Wyhe Skinner, Kirkland	James M. Bowers, George C. Miller, C. E. Watts
John Kay Martin, Seattle	George C. Miller, James M. Bowers, C. E. Watts
Donald Ainslie Palmer, Spokane	George H. Anderson, Arthur Betts, C. E. Watts
Max Singer Wright, Spokane	George H. Anderson, Arthur Betts, C. E. Watts
Walter Cyril Nalty (U. S. V. A.), Walla Walla	E. L. Whitney, Bryan M. Riley, C. E. Watts, Charles M. Griffith

WEST VIRGINIA

Frederick Rendell Whittlesey, Morgantown	G. R. Maxwell, Charles M. Bray, John N. Simpson, Walter E. Vest
Frank J. Holroyd, Princeton	Albert H. Hoge, Walter E. Vest, John N. Simpson

WISCONSIN

Charles Everard Lyght, Madison	J. S. Evans, William S. Middleton, Rock Sleyster
Benjamin J. Birk, Milwaukee	Andrew I. Rosenberger, John Huston, Rock Sleyster

TERRITORY OF HAWAII

Carl John Walfrid Wilen, Hilo	H. L. Arnold, A. G. Schnack, James G. Carr
Stewart Edward Doolittle, Honolulu	H. L. Arnold, A. G. Schnack, C. E. Watts
Richard D. Kepner, Honolulu	H. L. Arnold, A. G. Schnack, David Barr
Kyuro Okazaki, Honolulu	Edward L. Bortz, George C. Griffith, George Morris Piersol

CANADA

British Columbia

Samuel Edward Caldbick Turvey, Vancouver	J. C. McMillan, D. M. Baltzan, Fred T. Cadham
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New Brunswick

William Oswald McDonald, St. John	H. A. Farris, Colin G. Sutherland, D. Slater Lewis
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Ontario

Trenholm Lawrence Fisher, Ottawa	Warren S. Lyman, Arthur T. Henderson, Jabez H. Elliott
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Republic of Panama

Amadeo Vicente-Mastellari, Panama	Tomas Guardia, C. D. Briscoe, William M. James
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Dr Sydney R Miller then brought up the request of some Mexican candidates who had applied for the privilege of paying their initiation fee and dues in Mexican dollars, which are worth less than one-third of the equivalent in American currency. If the dues of Mexican members were accepted in Mexican dollars, the proceeds would be less than one-half the expenses of carrying such members on the Roster.

Upon motion by Dr O H Perry Pepper, seconded by Dr William D Stroud, and regularly carried, it was

Resolved, that members of the College in foreign countries, including Mexico, shall pay their fees and dues in American currency.

Dr David P Barr, Chairman of the Committee on Fellowships and Awards, reported that his Committee had found it desirable to choose the candidates for the Research Fellowship of the College at the autumn meeting of the Regents, rather than at the Annual Meeting. Seven excellent applicants had been given very careful consideration. The Committee recommended that the Research Fellowship for 1937-38 be awarded to Dr Robert Wallace Wilkens, now of Boston, Mass., for a year entirely devoted to research with Dr E Arnold Carmichael at the National Hospital, Queens Square, London, England.

Upon motion by Dr James Alex Miller, seconded by Dr William D Stroud, and regularly carried, it was

Resolved, that a Research Fellowship of the American College of Physicians, amounting to \$1,800.00 and available beginning July 1, 1937, be awarded to Dr Robert Wallace Wilkens.

The Committee on Fellowships and Awards further recommended that the John Phillips Memorial Award be given to Dr Richard E Shope of the Rockefeller Institute for Medical Research, Princeton, N J.

Upon motion by Dr David P Barr, seconded by Dr Jonathan C Meakins, and regularly carried, it was

Resolved, that the 1937 Award of the John Phillips Memorial Medal be made to Dr Richard E Shope.

Dr Barr reported that the Committee feels there is much room for profitable extension of the granting of Fellowships, and that this would afford one of the useful applications of the funds of the College.

Dr James H Means, Chairman of the Committee on the ANNALS OF INTERNAL MEDICINE, had no report to add to that already made by the Editor. He added, however, that the Committee would recommend to the Board of Regents that Dr Paul Clough be officially appointed Assistant Editor of the ANNALS.

Upon motion by Dr James H Means, seconded by Dr Robert A Cooke, it was *Resolved*, that the Board of Regents confirm the official appointment of Dr Paul Clough, of Baltimore, as Assistant Editor of the ANNALS OF INTERNAL MEDICINE.

Dr Jonathan C Meakins, Chairman of the Committee on Constitution and By-Laws, reported that his Committee had taken under consideration certain changes which should be recommended as amendments to the Constitution and By-Laws of the College.

PROPOSED AMENDMENTS TO THE CONSTITUTION

Article IV, "(a) Fellows. Fellows shall be members of the medical profession engaged as practitioners, teachers or research workers in Internal Medicine, who shall have been elected."

(change consists of the omission of "or in an allied specialty")

Article V, "Section 1. Associates shall be members of the medical profession engaged as practitioners, teachers or research workers in Internal Medicine, who shall have been elected."

(change consists of the omission of "or in an allied specialty")

On motion by Dr James Alex Miller, seconded by Dr William D Stroud, and regularly carried, it was

Resolved, that the Board of Regents approve of the amendments to the Constitution above outlined, and that notice of the proposal for these amendments shall be published in the *ANNAIS OF INTERNAL MEDICINE* in accordance with the requirements of the Constitution, Article VI

PROPOSED AMENDMENTS TO THE BY-LAWS

Article V, "Section 1 (a) He shall be more than 33 years of age,"

(change consists of a change in the age from 29 to 33)

"(c) He shall be a member in good standing in his local, state and national medical societies, except in the case of those not engaged in practice, such as full-time teachers or research workers in Internal Medicine,"

(change consists of elimination of "etc" and substituting "in Internal Medicine")

Article V, Section 2, line 6, eliminate "or by an Officer of the College, or by a member of the Board of Regents"

"Section 3 (a) In the case of practitioners without teaching or important hospital positions, or of candidates not engaged in the practice of Clinical Medicine, the candidate's nomination shall be accompanied by all necessary information as to fitness, by a satisfactory thesis, or by publications of sufficient number and character to qualify him for Fellowship"

(this is practically entirely reworded)

Note—In regard to outstanding persons in pathology, pharmacology, biochemistry, etc, these may be considered eligible under Article V, Section 3 (c), second paragraph, which should read as follows

"After 1931, a candidate for Fellowship shall be eligible only if already an Associate, except upon the high recommendation of the Committee on Credentials by reason of outstanding merit and accomplishment"

(this change consists of the rewording of the paragraph)

Article VI, "Section 1 He shall possess a Certificate from the American Board of Internal Medicine as having passed successfully the examinations of that Board"

(this is the insertion of an entirely new paragraph, entailing relettering the succeeding paragraphs—the present paragraph (a) becoming "(b)", (b) becoming "(c)", (c) becoming "(d)", (d) becoming "(e)", and (e) becoming "(f)")

Article VI, Section 1, old paragraph (c), new paragraph "(d) except in the case of those not engaged in practice, such as full-time teachers and research workers in Internal Medicine"

(this change consists of eliminating "those holding official hospital positions, etc" and substituting "in Internal Medicine")

Article VI, Section 1, old paragraph (d), new paragraph "(e)," line 6, "in Internal Medicine or in medical research"

(this change consists of the above substitution for "in one of the accepted branches of Internal Medicine or in Medical Research")

Speaking on the proposed changes to the By-Laws, Dr Meakins said the Committee had been faced with the problem of whether it should recommend changes requiring candidates to have passed successfully the examination of the American Board of Internal Medicine. There were three alternatives:

- (1) To make successful passage of the examination a prerequisite for Associateship,
- (2) To make successful passage of the examinations a prerequisite to Fellowship,
- (3) To ignore it altogether

The Committee felt that it would be better to make successful passage of the examinations a prerequisite to Associateship. This would assure the College that candidates for Associateship will have shown evidence of proper training, ethical standing, affiliations, etc., and would avoid the anomaly of admitting a candidate to Associateship who might later fail to pass the examination.

Upon motion by Dr James Alex Miller, seconded by Dr George Morris Piersol, and regularly carried, it was

Resolved, that the above proposed amendments to the By-Laws be submitted in writing to all members of the Board of Regents before its next meeting.

In the discussion of the proposed amendments to the By-Laws, there was divergence of opinion among Board members as to whether the requirement of certification by the American Board of Internal Medicine should precede Associateship, or be one of the requirements between Associateship and Fellowship. Several felt that Associates should be admitted much on the same plan as at present, with the exception of the amendment in the minimum age, but that before such an Associate may be eligible for Fellowship, he must obtain the certification of the American Board of Internal Medicine. By inserting this requirement between Associateship and Fellowship, the Committee on Credentials may eliminate the requirement of presenting case histories and autopsies, which have not proved a particularly satisfactory criterion in the past.

Dr Meakins, in discussing the underlying principles leading to the recommendation for amendments, in his report said, "In practically all the statements in the present Constitution and By-Laws, there is left considerable latitude as to research workers, laboratory workers, roentgenologists and the comprehensive term of an 'allied specialty'. A primary duty of the Credentials Committee is to review presented evidence, which would indicate that a candidate is sufficiently trained to practice Internal Medicine of a standard acceptable to the College. Whether, in the future, he should become engaged in hospital administration, medical research, roentgenology, etc., should not influence his future standing in the College. On the contrary, if his main activities have been for years in any of these branches of medical practice, no matter how high his reputation and accomplishments in these or other branches of medical practice, which are not directly concerned with the practice of Internal Medicine, they should not in any way justify his selection as an Associate of the College."

Dr Charles H Cocke, Chairman of the Board of Governors, inquired whether the Committee on Constitution and By-Laws had prepared any recommendation in regard to the appointment of alternate Governors.

Dr Meakins replied that his Committee had only considered the eligibility of candidates, but would take care of some provision for alternate Governors later on.

Dr Meakins asked for the opinion of the Board of Regents on a suggestion that there be created a group to be known as Emeritus Fellows, consisting of those who may retire, more or less, from the activities of the College on account of age.

During the discussion of the matter, the reaction seemed favorable, though no specific resolution was adopted.

Dr Walter L Biering, Chairman of the American Board of Internal Medicine, presented the following report

"The initiative for the formation of a certifying board for internists originated with the action of the American College of Physicians at the meeting of the Board of Regents in Philadelphia, April 30, 1935. At the meeting the Board of Regents voted to underwrite the organization expense of said Board up to the sum of \$10,000 00

"Concurrent action in the organization of the American Board of Internal Medicine was taken by the Section on the Practice of Medicine of the American Medical Association meeting in executive session at Atlantic City, June 14, 1935

"A joint Committee of Organization was formed comprising five representatives approved by President James Alex. Miller from the American College of Physicians, Meakins, Pepper, Barr, Richards, and Middleton, and four representatives, appointed by Chairman William J. Keir from the Section on the Practice of Medicine of the American Medical Association, Fitz, Irons, Musser and Biering, the latter was chosen as Chairman of the Joint Committee

"This Committee made its first report to the Board of Regents of the American College of Physicians at the meeting in Philadelphia, December 14, 1935, presenting a preliminary draft of the Constitution and By-Laws with an outline of the plan of examination and certification procedure

"The Articles of Incorporation of the American Board of Internal Medicine were filed for record on the 28th day of February, 1936

"At the meeting of the Board of Regents in Detroit, March 2, 1936, the organization of the American Board of Internal Medicine was officially approved and an appropriation of \$5,000 00 was voted to defray the expenses of the Board during the first year. At the meeting of the American Medical Association in Kansas City, May 12 and 13, 1936, the Board was given the final approval by the Section on the Practice of Medicine of the American Medical Association, the Advisory Board for Medical Specialties, and the Council on Medical Education and Hospitals of the American Medical Association

"With this final action, the American Board of Internal Medicine was duly organized and ready to begin operation

"The first meeting of the Board was held at the Palmer House, Chicago, June 14 and 15, 1936, at which the final details of organization were completed. The officers chosen for the first year were, Chairman, Walter L. Biering, Vice Chairman, Jonathan C. Meakins, Secretary-Treasurer, O. H. Perry Pepper, Assistant Secretary-Treasurer, P. M. Hutchinson, Attorney

"The terms of tenure of service of the members of the Board, as provided by the Articles of Incorporation, were determined by lot as follows

Representing the American College of Physicians

Dr Jonathan C. Meakins	1 year
Dr G. Gill Richards	1 year
Dr O. H. Perry Pepper	2 years
Dr William S. Middleton	2 years
Dr David P. Barr	3 years

Representing the Section on the Practice of Medicine of the American Medical Association

Dr Reginald Fitz	1 year
Dr Ernest E. Irons	2 years
Dr John H. Musser	3 years
Dr Walter L. Biering	3 years

"Attention is directed to Sections 5 and 7 of Article V of the Articles of Incorporation, which is as follows

"the membership of the Board shall be maintained at the ratio of five members from the American College of Physicians and four members from the Section on the Practice of Medicine of the American Medical Association and that at least three of the members of the Board from the American College of Physicians and two members of the Board from the Section on the Practice of Medicine of the American Medical Association shall be of professorial rank in approved medical schools of the United States or Canada"

Section 5, Article V, Articles of Incorporation

"The term of office of members of the Board succeeding the original Board members shall be three years and until their successors are elected and qualified, and no such member shall serve more than two consecutive three-year terms"

Section 7, Article V, Articles of Incorporation

"The following committees were named

Credentials and Qualifications

Dr Jonathan C Meakins, *Chairman*
 Dr William S Middleton
 Dr Ernest E Irons
 Dr Reginald Fitz

Examinations

Dr David P Barr, *Chairman*
 Dr O H Perry Pepper
 Dr G Gill Richards
 Dr John H Musser

"It was further decided at this meeting that the central office of the Board be maintained, for the present, at the office of the Chairman at 406 Sixth Avenue, Des Moines, Iowa

"During the months of July and August, 1936, in accordance with the directions of the Board, a publicity statement regarding the American Board of Internal Medicine, presenting its object and purposes with an outline of the special training and method of examination required of candidates for certification was released to 75 different medical journals, including the Annals of Internal Medicine, Journal of the American Medical Association, Canadian Medical Association Journal, British Medical Journal, all State Medical Society Journals, and special journals. The statement was published complete or in abstract in practically all of the Journals submitted, and quite a number added favorable editorial comment

"More complete information regarding the Board was later published in the form of a handbook

"The second meeting of the Board was held in Chicago, October 11 and 12, 1936, at which time the date for the first written examination was set for Monday, December 14, 1936, in different cities throughout the United States, and wherever possible, to be at or near the place where the applicant resides. The written examination shall consist of two parts

A A three-hour examination upon subjects in anatomy, physiology, pharmacology, pathology, biochemistry, bacteriology, and immunology, which are related to the proper understanding of Internal Medicine. This shall be held at 9 00 o'clock, a m., on the day of the examination

B A three-hour clinical examination of a general character to be held at 2 00 o'clock, p m, on the day of the examination

"The fees for examination have been set as follows

For Written and Practical Examination	\$40 00
For Certificate	10 00
For Certification without Examination	10 00

"At this meeting the following amendment to Article VI of the By-Laws, pertaining to special certification, was adopted

"To amend Article VI by striking out all of Article VI and substituting the following

ARTICLE VI

Special Certification

Advisors to the Board

Section 1 A There shall be appointed to the Board a group of leading internists, not to exceed two hundred and fifty (250) in number, who shall be known as Advisors to the Board They shall be certified without examination and their duties shall be to assist and advise the Board in the selection of Founders, the holding of examinations and such other duties as the Board may require of them

B They shall be selected by the Board as the Board may decide

Founders

Section 2 Until July 1, 1937, certificates of the American Board of Internal Medicine will be issued without examination to a limited number of specialists in Internal Medicine approved by the Board from the following

A Professors and associate professors of medicine in approved schools of medicine of the United States and Canada

B Physicians who have practiced the specialty of Internal Medicine for ten years, and are members or Fellows in good standing in one or more of the following special societies of internal medicine

- 1 American College of Physicians
- 2 Royal College of Physicians of Canada
- 3 Association of American Physicians
- 4 American Clinical and Climatological Association
- 5 American Gastro-enterological Association
- 6 American Society for Clinical Investigation
- 7 Central Society for Clinical Research

C Physicians who have practiced the specialty of Internal Medicine for fifteen years, and who are recommended by the Executive Committee of the Section on the Practice of Medicine of the American Medical Association

"It was moved that the Advisors to the Board be selected from the following

- 1 Professorial heads of departments of Internal Medicine of all the approved medical schools of the United States and Canada No such individual shall be eligible who is not an internist
- 2 Emeritus and active members of the Association of American Physicians who are internists

- 3 The officers and members of the Board of Regents for the year 1936-37 of the American College of Physicians who are internists
- 4 The Advisors to the Board must be 45 years of age or over, except those chosen under paragraph No 1 above
The Advisors to the Board shall be certified without examination upon the payment of the regular certification fee of \$10 00
- 5 An original member of the American Board of Internal Medicine shall, ipso facto, be certified without examination On termination of his membership on the Board he shall automatically become an Advisor to the Board

"It was the opinion of the Board that the Founders should be selected from applications addressed to the Board rather than from invitations sent out by the Board from a prepared list It was decided that the following letter be sent to prospective Founders

"The American Board of Internal Medicine, organized through the cooperation of the American College of Physicians and the Section on the Practice of Medicine of the American Medical Association, may issue a certificate of qualification without examination to a limited number of specialists, according to Section 2, Article VI of its By-Laws as follows

Section 2 Until July 1, 1937, certificates of the American Board of Internal Medicine will be issued without examination to a limited number of specialists in Internal Medicine, approved by this Board from the following

- A Professors and Associate Professors of Internal Medicine in approved schools of medicine of the United States and Canada
- B Physicians who have practiced the specialty of Internal Medicine for ten years, and are members or Fellows in good standing in one or more of the following special societies of Internal Medicine

- 1 American College of Physicians
- 2 Royal College of Physicians of Canada
- 3 Association of American Physicians
- 4 American Clinical and Climatological Association
- 5 American Gastro-enterological Association
- 6 American Society for Clinical Investigation
- 7 Central Society for Clinical Research

- C Physicians who have practiced the specialty of Internal Medicine for fifteen years, and who are recommended by the Executive Committee of the Section on the Practice of Medicine of the American Medical Association

"As all others must pass an examination it seems but reasonable to the Board that those who are admitted without examination should show evidence of qualifications equivalent, or better, to that which the Board requires of those who apply for admission through examination

"The Board will give consideration to those who graduated or took their internship prior to the date of the establishment of the present standards of the Council on Medical Education and Hospitals of the American Medical Association

"If you are desirous of submitting your name you are requested to fill out the enclosed form and return to the office of the Chairman in the enclosed envelope

for consideration by the Board as to your eligibility for certification without examination

" 'A registration fee of \$10 00 must accompany this application ' "

"In conformity with the action of the Board at its last meeting on October 11-12, 1936, the list of Advisors to the Board was completed as selected from the following, in accordance with the method previously stated

- 1 Professorial heads of departments of Internal Medicine of all approved medical schools of the United States and Canada
- 2 Emeritus and active members of the Association of American Physicians
- 3 Officers and members of the Board of Regents for the year 1936-37 of the American College of Physicians who are internists

All Advisors to be 45 years of age or over, except those chosen as professorial heads of departments of Internal Medicine

This list comprised 188 names. An individually signed letter was sent to each Advisor selected of the form adopted at the last meeting. The response was very gratifying as 168 favorable replies were received, each expressing interest in the purpose of the Board and appreciation for the selection. Eight of the Advisors selected had retired from active practice and preferred not to serve. Of the remaining 160, all but 6 have remitted the registration fee of Ten Dollars "

(Dr Bierring at this point presented the list of Advisors)

"The selection of a Founders list has not progressed as rapidly. Letters of the form adopted at the last meeting have been mailed to 1,500 Fellows of the American College of Physicians during the past week. Each letter was signed personally by the Chairman and an application enclosed for certification without examination, a statement of qualifications required of candidates taking the examination, and a business return envelope

"Letters are now being prepared for members and Fellows of the following societies, who are not Fellows of the American College of Physicians or Advisors of the Board

- 1 Royal College of Physicians of Canada
- 2 Association of American Physicians
- 3 American Clinical and Climatological Association
- 4 American Gastro-enterological Association
- 5 American Society for Clinical Investigation
- 6 Central Society for Clinical Research

"In addition, the professorial heads of Internal Medicine, who are Advisors, have been asked to submit a corrected list of professors and associate professors of Internal Medicine in their respective schools, and answers have been received from all, with a few exceptions

"The entire list of Founders to be considered will probably comprise 2,500 names

"The preparations for the first written examination on December 14, have proceeded in accordance with the plans adopted by the Board at the last meeting. Advisors of the Board have been assigned to serve as supervisors of the examination in the different cities with two exceptions—Bismarck, N D, and Orlando, Fla. (In Bismarck, N D, the State Health Officer, Dr Maysil Williams will act as supervisor, and in Orlando, Fla, Dr Meredith Mallory, F A C P, will act in a similar capacity)

"In each instance the candidate has been assigned a registration number, which will be retained throughout all the examinations, and directed by telegram to report at the designated place of examination on Monday, December 14, 1936, at 9 00 o'clock, a. m. A copy of this telegram is sent to the supervisor concerned for purposes of identification.

"A set of examination questions of Part 1 and Part 2 has been sent to each supervisor in separately sealed envelopes by special delivery mail. A supply of blank examination paper arranged in booklets has also been sent to each supervisor.

"The directions for conducting the written examination as submitted to each supervisor are as follows:

"The examination will be in charge of the Advisor selected by the Board, who will observe the following directions and regulations:

- 1 Hold the examination on the day and hour prescribed
- 2 Admit to the examination only those candidates who hold letter of admission from the Board
- 3 Ascertain that the identification number given by each candidate, which is to be used on all of the answer papers, corresponds with the number assigned by the Board
- 4 Break the seal of the question papers in the presence of the candidate at the beginning of each session of the examination
- 5 Collect the answer papers after each session and at the close of the examination period, enclose these with identification forms, unused examination paper and questions, in addressed envelopes, and forward by express, collect, to the office of the Chairman, Room 1210, 406 Sixth Avenue, Des Moines, Iowa, U S A."

(Dr. Bierring stated at this point that there had been 53 candidates approved for admission to the first written examination, and gave the assignment of candidates with respect to the cities and examiners throughout the United States.)

"The Committee on Credentials and Qualifications did not approve eight applicants, because of insufficient qualifications. Each of the applicants was refunded \$30 00 of the examination fee, \$10 00 being retained as the registration fee.

"Four applicants having paid the examination fee of \$40 00, upon further review by the Committee were recommended for certification without examination, and a refund will be made of \$30 00 each. Three applications submitted for certification without examination, previously considered by the Board and resubmitted to the Committee on Credentials and Qualifications, were subsequently recommended for reference to the Executive Committee of the Section on the Practice of Medicine of the American Medical Association for further action. These have been forwarded as directed, but to date have not been returned.

"Four applications have been received to date for the second written examination to be held during March, 1937.

"The amount received by the Chairman for registration and examination fees, to date, is \$4,310 15, of which \$250 00 has been refunded, leaving a balance of \$4,060 15 deposited in the Bankers Trust Company Bank, Des Moines, Iowa, to the account of the American Board of Internal Medicine, Walter L. Bierring, Chairman. It is to be noted that fees collected are to a certain extent a liability held in escrow until all examinations and certification procedure have been completed.

"All current expenses of the Board are paid out of the allotment of \$5,000 00 granted by the American College of Physicians. Up to and including November 30, \$3,761 12 has been expended. The estimated expense of this meeting and of current

expenses to and including December 31, 1936, is \$875 00, making a total of \$4,636 12, leaving an approximate balance January 1, 1937, of \$363 88

"In view of the increasing volume of work connected with the present operation of the Board and two meetings in prospect, April and June, 1937, it is estimated that at least \$3,000 00 will be required to carry on until July 1, 1937. By this date it is reasonable to anticipate a considerable fund will be available from fees retainable

"At the meeting of the American Board of Internal Medicine on December 12, 1936, the Chairman was directed, on behalf of the Board, to make application to the Board of Regents of the American College of Physicians for an additional grant of \$3,000 00 to be available to June 30, 1937, it being understood that this grant of \$3,000 00 in addition to the former grant of \$5,000 00 is to be considered as a loan to the American Board of Internal Medicine to be refunded as soon as definite funds are available"

In conclusion, Dr Bierring, on behalf of the American Board of Internal Medicine, thanked the Board of Regents for the wise counsel and financial aid which had been extended

On motion by Dr James Alex Miller, seconded by Dr James E Paullin, and regularly carried, it was

Resolved, that the Board of Regents of the American College of Physicians express their appreciation of the progress that has been made by the American Board of Internal Medicine, and that the College approve the appropriation of the further amount of \$3,000 00

Dr William D Stroud submitted the following report, as Treasurer

"Investments in Bonds, approximately	\$80,000 00
Investments in Preferred Stocks	4,427 00
Investments in Common Stocks	15,500 00
Uninvested Cash in Endowment Fund	527 00
Cash in General Fund	27,977 00

"About \$1,500 00 had been received from closed banks in Pittsburgh on account during the past year

"The total assets, including investments, cash and the College Headquarters, approximate \$183,000 00"

On motion by Dr James Alex Miller, seconded by Dr James E Paullin, and regularly carried, it was

Resolved, that the report of the Treasurer be accepted and filed. Dr James Alex Miller made a detailed report for the Finance Committee

"The analysis of the Girard Trust Company of our securities was considered, and it was voted to approve the recommendations of their report

"It was voted to withdraw our savings account and to invest it at some such good time in income bearing securities, after receiving recommendations from the Girard Trust Company, which would be circulated to the members of the Finance Committee

"It was recommended that the Board of Regents approve the expenditures for taxes and insurance on the new headquarters as an item of upkeep, amounting to \$1,109 63, which temporarily had been drawn from the funds appropriated for purchase and furnishings

"It was recommended that the Board of Regents set up a repair and replacement fund, which it was suggested should amount to \$500 00 a year

"We would report that according to the estimate of the upkeep for 1937 in the new headquarters, the upkeep expenses will be \$3,480 00, and that the capital outlay, \$62,000 00 at 4 per cent interest, would be \$2,480 00, so that the total upkeep and rental for the new headquarters would be approximately \$6,000 00 a year

"The Finance Committee considered in detail the 1937 budget presented by Mr E R Loveland in behalf of various departments, and recommends it for approval

by the Regents as submitted, with estimated receipts of \$77,500 00 and estimated expenditures of \$60,257 67, an estimated balance of \$17,242 33

Respectfully submitted,

JAMES ALEX MILLER, *Chairman,*
Committee on Finance"

Upon motion by Dr Francis M Pottenger, seconded by Dr William Gerry Morgan, and regularly carried, it was

Resolved, that the report of the Finance Committee be approved, and the Committee authorized to make the sales and purchases recommended, further that the Treasurer be authorized to withdraw the funds from the savings accounts, and to invest the funds in securities to be approved by the Finance Committee, further that the Board of Regents approve the expenditures for taxes, insurance, etc, on the new headquarters, amounting to \$1,109 63, and that this appropriation be added to the original appropriations for 1936, further that the Board of Regents approve the setting up of a repair and replacement fund of \$500 00 per year—this amount merely being set aside if needed, but not otherwise withdrawn from invested funds, further that the detailed budgets recommended by the Finance Committee for 1937, with estimated receipts of \$77,500 00 and estimated expenditures of \$60,257 67, be approved

Dr Ernest B Bradley, President, outlined the plans for the St Louis Session, April 19-23, 1937, so far as the General Program and Convocation were concerned Dr David P Barr, General Chairman, discussed the tentative program for the clinics, and Mr Loveland, Executive Secretary, reported upon the business arrangements Almost all the available exhibit space has been disposed of and all details have been arranged with the headquarters' hotel, the New Jefferson

Dr James Alex Miller, Chairman, presented a report of progress for the Committee on Future Policy for the Development of Internal Medicine This Committee had considered the comparative value of the John Phillips Memorial Award, the advisability of inviting speakers and lecturers from abroad and from the United States to give lectures under the auspices of the College and at its expense, and the idea of establishing a revolving fund to help younger practitioners to meet the requirements for registration as internists The Committee had also considered the possibility of maintaining a directory of postgraduate activities to be published in the *ANNALS*

No action had been taken on any of these suggestions

Dr James Alex Miller also brought up the situation concerning the National Conference on Nomenclature of Disease He stated that the Conference had published a Nomenclature of Disease which is now widely used, and which meets with wide approval Through some oversight, an invitation to the College to participate in this work had not been accepted by the College in the year 1929 On behalf of the Chairman of the Executive Committee of the National Conference, Dr Miller renewed the invitation to the College to cooperate with the long list of associations comprising the Conference

Dr Miller moved that the College lend its name in cooperation to the National Conference on Nomenclature of Disease

This was seconded by Dr William D Stroud, and regularly carried

On motion by Dr George Morris Piersol, seconded by Dr Walter L Bierring, and regularly carried, it was

Resolved, that the College make an appropriation of \$1,000 00 for the aid of this worthy work

On motion by Dr William D Stroud, seconded by Dr Sydney R Miller, it was moved that the American College of Physicians establish another Research Fellowship of \$1,800 00 for one year, July, 1937, to June, 1938

In the discussion of the motion, it was agreed that the action was not to establish two Fellowships permanently, that in some years there might be more and in other years possibly none The motion was carried

On the recommendation of Dr David P Barr, on behalf of the Committee on Fellowships and Awards, by a motion made, seconded and regularly carried, it was

Resolved, that this Fellowship be awarded to Dr Abner McGhee Harvey, now of the Johns Hopkins Hospital, Baltimore, Md

In the absence of Dr James D Bruce, Chairman, Dr Jonathan C Meakins reported for the Committee on College Records of Members The Committee, utilizing the form now in use in connection with the publication of the annual Directory, suggested an appropriate form which by resolution was adopted

Dr James Alex Miller, on behalf of Dr Walter W Palmer, Governor for eastern New York, Dr Luther F Warren, Regent, Dr Robert A Cooke, Regent, and himself as Regent, presented the following invitation for the 1938 Annual Session of the College to be held in New York City

"We, the officers of the American College of Physicians, who reside in New York City, desire to request the favorable consideration of the Board of Regents of an invitation to hold the meeting of the College in 1938 in New York City

"Preliminary inquiries have established the fact that we would be able to obtain suitable hotel and auditorium facilities here and also that we would have the whole-hearted cooperation of the large medical centers for the presentation of the clinical programme

"The situation in New York is not one that lends itself to the usual method of presentation of an invitation for a meeting of the College, that is, it is not customary for organizations such as the County Medical Society, the Academy of Medicine or individual hospitals to invite medical organizations to meet in New York City Consequently, we are asking you to consider this invitation as representing the hearty feeling of the Fellows of the College in New York City and of the principal hospital and educational institutions which would participate in the meeting

Very respectfully yours,

(Signed) WALTER W PALMER, *Governor*

(Signed) LUTHER F WARREN, *Regent*

(Signed) JAMES ALEX MILLER, *Regent*

(Signed) ROBERT A COOKE, *Regent*"

Upon motion by Dr James H Means, seconded by Dr Robert A Cooke, and regularly carried, it was

Resolved, that members of the Board of Regents shall tender a Dinner to members of the Board of Governors at the St Louis Session, as was done at the last Annual Session in Detroit

President Bradley inquired if there was any desire to change the ruling with regard to any allowances for traveling expenses of the Regents for the Annual Sessions There was a consensus of opinion that this should stand as at present, namely, their return convention and pullman fare, without any allowance whatsoever for hotel or other expenses

Adjournment

Attest (signed) E R LOVELAND,
Executive Secretary

OBITUARIES

DR HENRY S PLUMMER

DR HENRY S PLUMMER was born in Hamilton, Minnesota, on March 3, 1874, the son of Dr Albert Plummer and Isabelle Plummer. He died in Rochester, Minnesota, on December 31, 1936, of cerebral thrombosis. His early education was obtained in the local public schools and in the University of Minnesota. He attended the Medical School of Northwestern University, from which he received the degree of Doctor of Medicine in 1898. His first three years of practice were spent with his father in Racine, Minnesota, and in 1901 he entered The Mayo Clinic, where he continued the practice of medicine until his death.

In the early years of his practice he became deeply interested in roentgenology, bronchoscopy and esophagoscopy. His early work in the treatment of cardiospasm and esophageal stricture resulted in an important contribution to medicine, and his hydrostatic dilator and esophageal sounds, first designed and made by him in his own workshop, are still in use in the treatment of those conditions. Throughout his years of medical practice his greatest interest was in the function and diseases of the thyroid gland. Early in his experience, his keen clinical observations allowed him to define the two entities, exophthalmic goiter and hyperfunctioning adenomatous goiter. His development of a "two-product hypothesis" in exophthalmic goiter led, in 1921-22, to the demonstration of the beneficial effect of the administration of iodine to patients with exophthalmic goiter. This, his most outstanding contribution, has been responsible for a marked and general lowering in the mortality of exophthalmic goiter. His opinions on diseases of the thyroid are accepted as authoritative both in this country and abroad. His contributions to the literature were prepared with meticulous care, and were always the result of exhaustive study. He was apt, however, to leave unpublished a great deal that he knew and understood. It was this propensity that enabled him to teach his associates more by intimate contact and direction than by what he put into the literature.

Dr Plummer's interests were, however, not limited to medicine. Whatever he became interested in he studied in the greatest detail. He gave much thought to the improvement of facilities for the care of patients, and the utilitarian features of the design of The Mayo Clinic building came largely from his mind. His opinions were sought on a variety of subjects, among them horticulture, building construction, and engineering.

Dr Plummer was elected a Fellow of the American College of Physicians March 11, 1922, and served as a Regent of the College from 1923 to 1927. He was also a Fellow of the American Medical Association. He held membership in the Association of American Physicians, Association for the Study of Internal Secretions, American Association for the Advance-

ment of Science, American Association for the Study of Goiter, American Gastro-Enterological Association, Medical Library Association, American Association for Thoracic Surgery, American Public Health Association, Royal Society of Arts, Minnesota Pathological Society, Southern Minnesota Medical Association, Central Interurban Clinical Club, Minnesota Society of Internal Medicine, Central Society for Clinical Research, Minnesota State Medical Association, Olmsted-Houston-Fillmore-Dodge County Medical Society, Alumni Association of The Mayo Foundation, Sigma Xi, Alpha Omega Alpha, Minnesota Horticultural Society, University Club of Rochester, and St Paul Athletic Club

In 1920-21 he was the chairman of the Section on Practice of Medicine of the Scientific Assembly of the American Medical Association. In 1933 he was elected President of the American Association for the Study of Goiter, and in 1935 Northwestern University conferred on him the degree of D Sc (honoris causa). Since 1915 he had been Professor of Medicine, The Mayo Foundation, Graduate School, University of Minnesota.

Dr Plummer was a keen observer and had a remarkable ability to correlate the masses of facts which he accumulated. He had great knowledge of human problems, and his philosophy of medicine was tempered by a wide humanitarian outlook. His sense of fairness was outstanding. In him were combined to a remarkable degree the finest characteristics of clinician and investigator. His life was devoted to a constant and unusually productive effort to improve the quality of the care of the sick. By his death Medicine has lost a prodigious worker and a great physician, and his associates have lost a friend, a guide, and an inspiration.

SAMUEL F. HAINES, M.D., F.A.C.P.

DR. JAMES ALLISON HODGES

JAMES ALLISON HODGES died on December 15, 1936, at the age of 78. Born in North Carolina, his early education was obtained at preparatory schools and at Davidson College in that State; in 1883 he was graduated from the department of medicine of the University of Virginia. After practicing several years in Fayetteville and Wilmington, N. C., he moved in 1893 to Richmond and became affiliated with the newly organized University College of Medicine as Professor of Anatomy. In 1896 he became Professor of Nervous and Mental Diseases and for a time served as President of that institution. Upon the merging of the University College of Medicine with the Medical College of Virginia in 1914 he became Professor of Clinical Neurology and Psychiatry in the latter, a position he held up to 1927, when he became Professor Emeritus. In addition to an extensive practice and teaching, he operated the Hygeia Hospital, a private institution, from 1903 to 1920, and for a number of years was medical director of a large life insurance company.

Dr Hodges took an active and prominent part in a number of medical organizations. He was one of the founders in 1897 of the Tri-State Association of Virginia and the Carolinas, and in 1918 its President. In 1923 he served as President of the Richmond Academy of Medicine. In the Medical Society of Virginia he was always active, serving as President in 1930 and contributing regularly toward its welfare and advancement. In 1916 he became a Fellow of the infant American College of Physicians and might be considered one of its charter members.

A man of imposing presence, tremendous energy and great ability, Dr Hodges was always ready to assist in any undertaking designed for the advancement of medicine or the betterment of society. A gifted speaker, his services were in much demand and numerous worthy causes profited from his efforts.

Following a coronary thrombosis a few years ago, Dr Hodges' activities have been greatly restricted, but he continued up to the time of his death in full possession of his faculties and manifested a lively interest in contemporary affairs, both professional and civic.

J MORRISON HUTCHESON, M D , F A C P ,
Governor for Virginia

DR ERNEST E LAUBAUGH

DR ERNEST E LAUBAUGH, Fellow and Governor of the American College of Physicians for the State of Idaho, died, December 13, 1936, after a four-day illness from influenza-pneumonia, at the age of forty-nine years.

Dr Laubaugh was born at Shickshinny, Pennsylvania, August 20, 1887. He attended the public schools of Philadelphia and received his medical degree from the Medico-Chirurgical College of Philadelphia in 1909. He interned at the Mercy Hospital, Wilkes-Barre, Pennsylvania, 1909, and the Philadelphia General Hospital, 1910-11. He continued with this institution as Scrologist during 1912-13. During 1911-12, he was Assistant Demonstrator in Physical Diagnosis, and during 1912-13, Assistant in the Department of Neurology of the Medico-Chirurgical College. In 1913, he accepted an appointment as Bacteriologist on the Idaho State Board of Health, which appointment he held until 1917. During 1919-20, he was Medical Advisor to the Department of Public Health of Idaho. From 1919-23, he was Consultant to the U S Veterans Hospital in Boise. At the time of his death he was a member of the staff of the St Alphonsus and St Luke's Hospitals in Boise.

During the World War, he was a first lieutenant in the U S Army, later advancing to a captaincy, and was stationed at the Port of Embarkation, Newport News, Virginia.

Dr Laubaugh was a member of the Omega Upsilon Phi fraternity, Boise Physicians Club, Idaho State Medical Association, Southwestern Medical Society of Idaho, American Society of Bacteriologists, American

Heart Association, he was a Fellow of the American Medical Association, the American Society of Clinical Pathologists, and had been a Fellow of the American College of Physicians since 1927

He made a number of contributions to medical literature and had held a distinctly outstanding position as an internist in Idaho and the northwest. He was a member of the Episcopal Church, American Legion and the Masonic fraternity. He is survived by his widow, Mrs Beth Laubaugh, a son, James E Laubaugh and a daughter, Lucile Laubaugh.

Those who knew him remember him as a quiet, genial, kindly and earnest physician, unassuming in manner, yet determined to keep abreast of the latest developments in his specialty and to give his patients always the benefits of his skill and care. Many Fellows of the College who took the official cruise to Cuba and Panama, following the last New Orleans Session of the College, will more vividly remember Dr Laubaugh as one of the party. He had been a Governor of the College for the State of Idaho since 1928, and had served the College with the same efficiency, earnestness and integrity as he practiced his profession.

E R LOVELAND,
Executive Secretary

DR WILLIAM FREDERICK WEGGE

WILLIAM FREDERICK WEGGE (Fellow), Milwaukee, Wisconsin, died on November 20, 1936, at the age of seventy-three.

Dr Wegge, a native of Wisconsin, first studied dentistry at Baltimore University. After practicing that profession for a few years he returned to the University of Maryland School of Medicine, from which he was graduated in 1886. He took several post-graduate courses in Austria and Germany, specializing in mental disorders. Upon his return from Europe he did general practice for a short time and then held the position of Superintendent at the Northern Hospital for the Insane at Winnebago. Following his service at the State Hospital he located in Milwaukee, limiting his practice to neuropsychiatry. He was for many years Professor of Neuropsychiatry at the Milwaukee Medical College, and at the time of his death was Emeritus Director of the Division, and Professor of Clinical Neurology, Marquette University School of Medicine. He was a member of the Medical Society of Milwaukee County, the State Medical Society of Wisconsin, the American Medical Association, and Past-President of the Milwaukee Neuropsychiatric Society. He was elected a Fellow of the American College of Physicians in 1930.

ROCK SLEYSER, M D , F A C P ,
Governor for Wisconsin

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CIRCULATORY STUDIES ON ANOXEMIA IN MAN WITH RESPECT TO POSTURE AND CARBON DIOXIDE¹

By E. GELLHORN, M.D., Ph.D., *Chicago, Illinois*

Mosso,²² Margaria,²⁰ Childs, Hamlin and Henderson⁴ noted that the effects of anoxemia can be alleviated by breathing low concentrations of CO₂. In several studies (Gellhorn^{7,8}) we have confirmed and extended these observations on a quantitative basis. It was shown in particular that the effects of anoxemia on various processes occurring in the human central nervous system can be offset by inhaling 3 per cent CO₂ during the period of anoxemia. This effect was thought to be due mainly to circulatory and respiratory adjustments. This idea is supported by the fact that under the influence of CO₂ the circulation through the brain is specifically increased (Cobb and Fremont-Smith,⁹ Lennox and Gibbs,¹⁰ Gibbs, Gibbs and Lennox,¹² and Schmidt²⁴). Furthermore, due to increased muscle tonus, there is an improvement in general circulation indicated by a rise in venous pressure (Henderson and collaborators¹¹). Other factors will be discussed below.

The present investigation was undertaken with the aim of establishing, in the human, direct proof for the improvement of the general circulation by CO₂ under the conditions of oxygen deficiency. Since the circulation in the brain, in which the symptoms of oxygen deficiency become first manifest, is primarily dependent on the systemic blood pressure, comparative blood pressure studies on the effect of oxygen deficiency with and without the simultaneous administration of CO₂ seemed appropriate. The fact that under ordinary circumstances oxygen want causes only very slight changes in the systemic blood pressure (Raab,²³ Gellhorn and Spiesman,^{9,10} Christensen and Krogh,⁵ and Herbst and Manigold¹⁶) does not invalidate this argument. In order to show the influence of one particular factor on the blood pressure which is normally maintained by the integrative action of several peripheral and central nervous factors and by the O₂—and CO₂—tension of the blood,

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From the Department of Physiology, College of Medicine, University of Illinois

it seemed appropriate to study the circulatory system under a certain strain which might make the whole system more labile. If such a condition were found it was not improbable that the beneficial effect of CO_2 , which was so distinct in our investigations on various functions of the central nervous system under the influence of oxygen want, would also become evident in regard to blood pressure.

As we now know, the maintenance of the blood pressure is dependent to a large extent on the functioning of carotid sinus and depressor reflexes (Hering,¹⁶ Koch,¹⁸ Heymans¹⁷). When the pressure falls in the aorta and in the carotid artery these reflexes are evoked and the normal blood pressure is restored. Therefore changes in posture are ordinarily not accompanied by significant changes in systemic blood pressure. Under conditions of oxygen want, however, the blood pressure falls considerably in the erect posture, whereas the same degree of oxygen want does not significantly alter the blood pressure in a recumbent position (Mateeff and Schwarz²¹). For this reason the effect of CO_2 under conditions of oxygen deficiency was studied on humans in the erect posture.

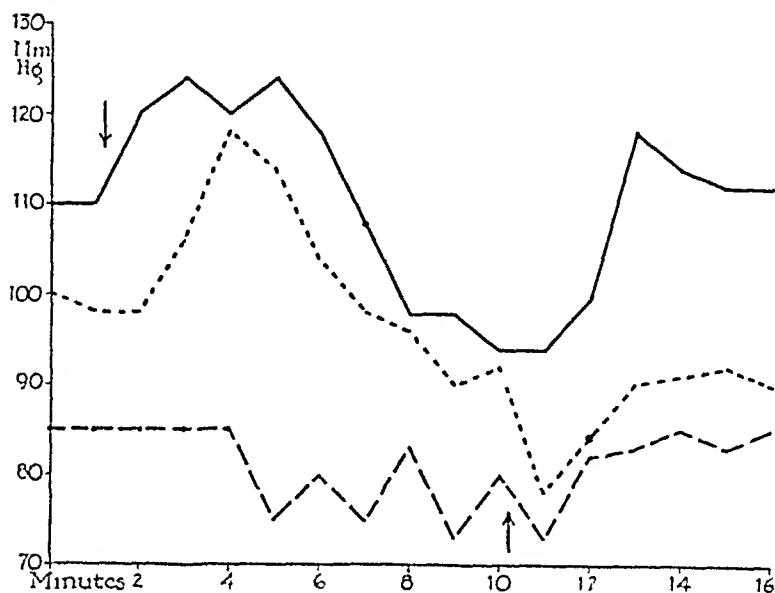
METHOD

The pulse was counted at one minute intervals and blood pressure readings, systolic and diastolic, were taken by two experimenters while the experimental subject was standing and inhaling a gas mixture from a Douglas bag. The gas mixture was prepared with the aid of a Sargent gas meter and frequently analyzed for O_2 and CO_2 . The duration of the experiment was seven to twelve minutes. It was preceded and followed by a control period in which the experimental subject inhaled air. The shift from air to the gas mixture and from that back to air was performed without the knowledge of the experimental subjects. The subjective and objective symptoms observed during the experiments were protocolled immediately after the experiments. The observations were made on 12 healthy experimental subjects, medical students of the ages of 20 to 25, most of whom had served as experimental subjects in experiments in which the effect of O_2 deficiency was studied in regard to various functions of the central nervous system. In some cases the experiments were repeated several times on the same subject without any essential difference in the results.

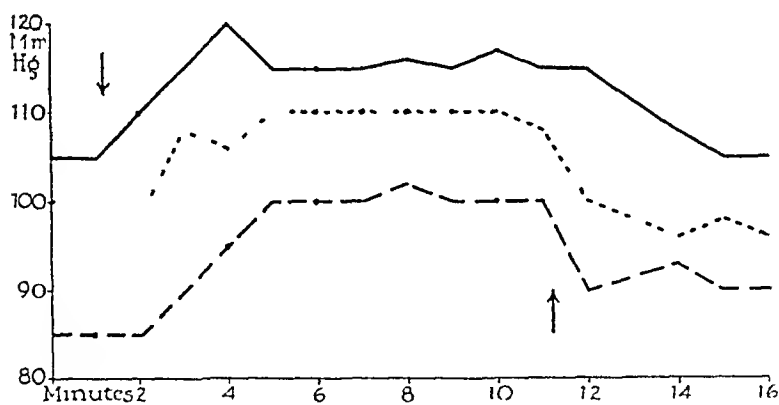
RESULTS

Figures 1a and 1b show the effect of 8.5 per cent O_2 , and 8.5 per cent O_2 plus 3 per cent CO_2 , respectively, on pulse and blood pressure during a period of nine to ten minutes. In the 8.5 per cent O_2 experiment the systolic blood pressure rises by 10 to 14 mm. mercury during the first three minutes, and then falls gradually below the control value. At the same time the pulse rate which had risen considerably also shows a drop, which even continues for a short time after the readmission of air. The diastolic

blood pressure shows only a slight decrease. All changes were nearly completely reversed in the first five minutes following the period of O_2 want. The characteristic feature of this and similar experiments is the fact that the increase in blood pressure and pulse rate resulting from anoxemia does not persist throughout the experiment but that a collapse-like reaction occurs



1a



1b

FIG 1a and 1b 85 per cent O_2 and 85 per cent O_2 plus 3 per cent CO_2 respectively between arrows (Subject He, erect posture) (Figs 1-4 and 6-7 — systolic blood pressure, ---- diastolic blood pressure, pulse rate per min. Abscissa time in min, ordinate blood pressure in mm Hg and pulse rate per min.)

characterized by a more or less abrupt decrease in systolic blood pressure and pulse rate, accompanied by considerable weakening of the pulse, pallor and dizziness. In some experiments showing the same type of reaction a sudden collapse sets in and the pulse becomes imperceptible but the recovery is fast.

Comparing with this experiment the results obtained from the same subject under the conditions of the same degree of oxygen want, but in the presence of 3 per cent CO_2 , we see an enormous contrast (figure 1b). The systolic blood pressure is slightly elevated and remains so throughout the whole period of O_2 want. The changes in pulse rate are slight, but the increase observed also persists until air is readmitted. The diastolic blood

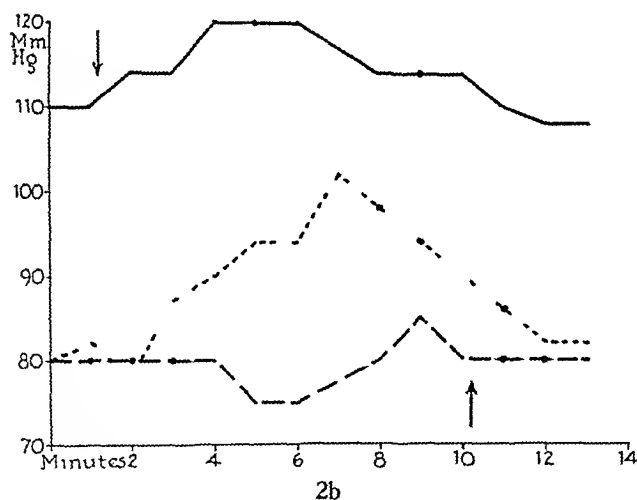
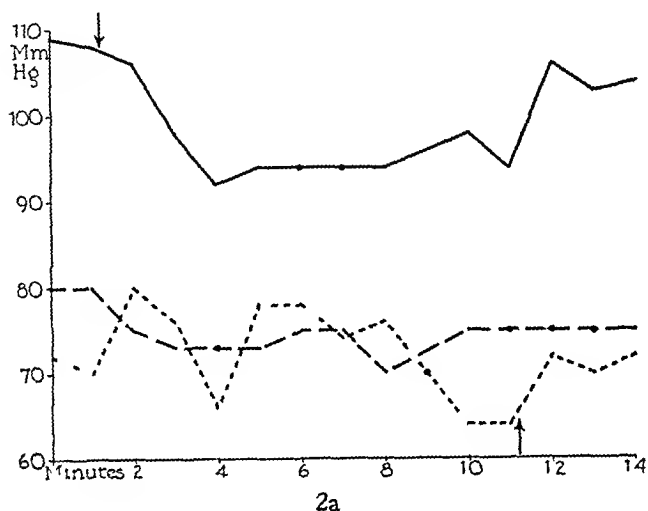


FIG 2a and 2b 85 per cent O_2 and 85 per cent O_2 plus 3 per cent CO_2 respectively between arrows (Subject Fa, erect posture)

pressure shows an increase during the experiment. The subjective experiences of the subject are equally striking. In general the subjects feel fairly well except for a slight dizziness or feeling of warmth. In some cases no symptoms whatever are observed, even though certain of these cases had experienced severe symptoms in the absence of 3 per cent CO_2 .

Figure 2 represents the record of an experiment in which the circulatory adjustment under oxygen want is still poorer than in the first case (figure 1)

After admission of 8.5 per cent O_2 in erect position the systolic blood pressure gradually falls and remains fairly low during the period of anoxemia. The pulse rate shows irregular variations without any definite tendency. The diastolic blood pressure is practically unaltered. In contrast to this reaction we observe, in the corresponding oxygen deficiency experiment in which 3 per cent CO_2 was also administered, that the fall in blood pressure is

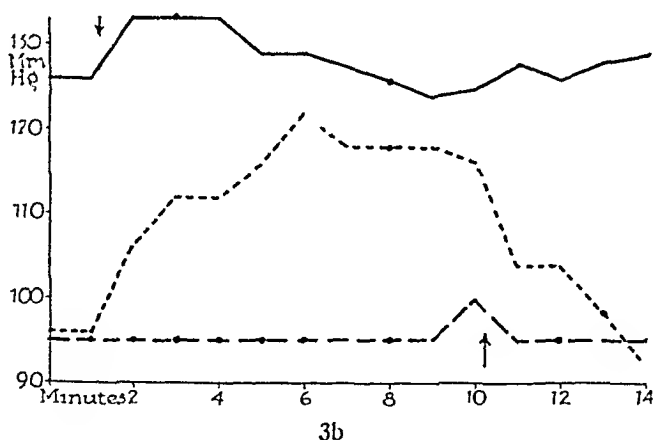
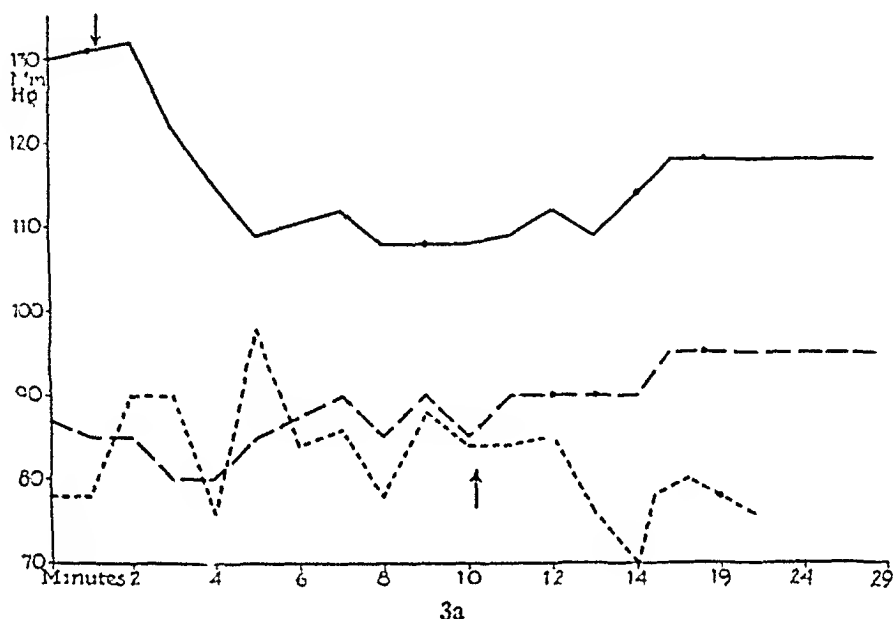


FIG 3a and 3b 8.5 per cent O_2 and 8.5 per cent O_2 plus 3 per cent CO_2 respectively between arrows (Subject St, erect posture)

not only completely prevented but that the blood pressure remains elevated throughout the experimental period. Furthermore, a distinct increase in pulse rate occurs during this time.

A very similar type to that shown in figure 2 is illustrated in figure 3. The main difference between the two experimental subjects is the fact that the systolic blood pressure is considerably higher to begin with in the case

of subject S (figure 3) than in that of F (figure 2). It is striking to see that the systolic blood pressure falls continuously until it reaches a certain equilibrium and that permanent changes in pulse rate are absent in anoxemia, whereas in the presence of 3 per cent CO_2 a marked increase in pulse rate occurs and the fall in systolic blood pressure is completely prevented. The difference in the two subjects whose curves are illustrated in figures 2 and 3 is, as was mentioned, a difference in the absolute values for the systolic pressure. This seems to be of considerable importance. S, whose systolic blood pressure is considerably greater than that of F, shows far less symptoms than the latter, obviously for the reason that the circulation of the brain can be maintained to a better degree in the first case than in the second,

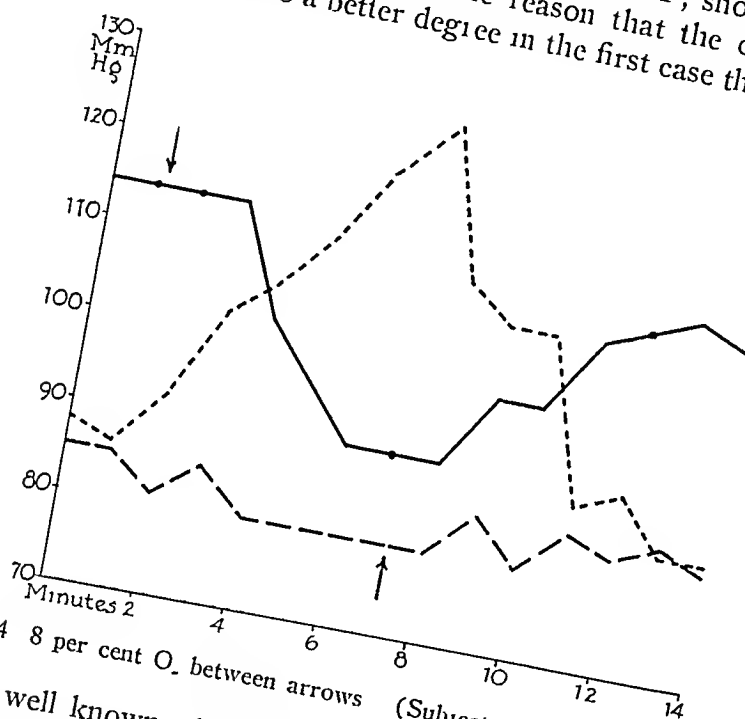


FIG 4 8 per cent O_2 between arrows (Subject G, erect posture)

since, as it is well known, the degree of circulation through the brain is largely dependent on the level of the systemic blood pressure (Starling²⁶). The experiments discussed so far have one feature in common, namely, the fall in the systolic blood pressure during anoxemia is accompanied by a decline in the pulse rate or by a complete failure of the organism to increase its pulse rate under anoxemia. But this is not always the case. Figure 4 shows a record in which a very marked drop in systolic blood pressure occurs during anoxemia which produces a condition approaching collapse, while at the same time the pulse rate increases tremendously. We are probably not mistaken in assuming the circulatory conditions in this case to be similar to those described in the other experiments, since in both types of reactions collapse may ensue. That a very rapid pulse is associated with a decrease in minute volume, has frequently been shown to be true under conditions of oxygen want (Barcroft²⁷).

As the description of various experiments has shown, the main difference in the experiments with 8 and 8.5 per cent O_2 with and without 3 per cent CO_2 lies in the fact that the systolic blood pressure falls in anoxemia to a relatively low level, thereby endangering the blood circulation through the brain. In the presence of 3 per cent CO_2 , however, this reaction is more or less completely prevented, and the systolic blood pressure remains either normal or even slightly elevated. A summary of several such experiments is presented in figure 5.

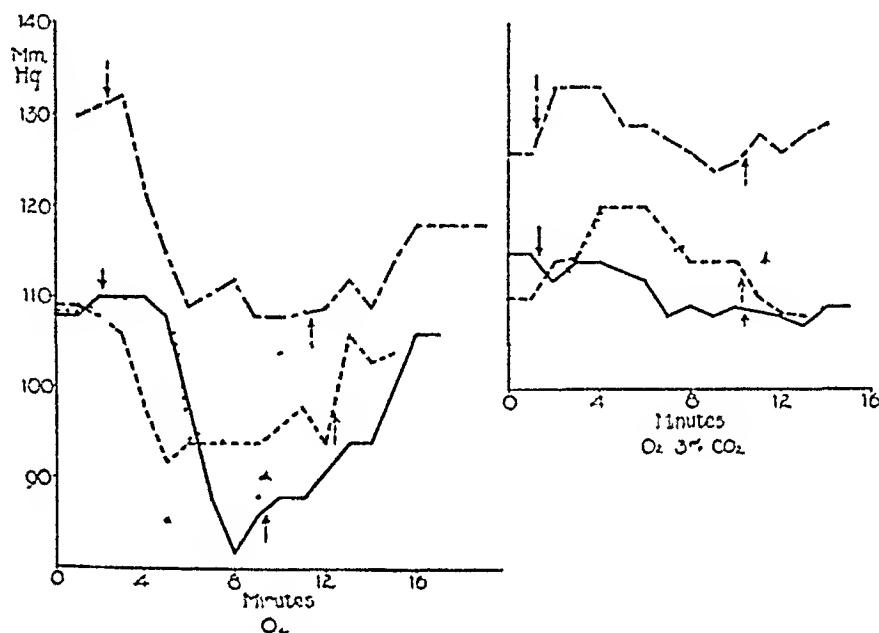


Fig 5 The effect of 8.5 per cent O_2 and 8.5 per cent O_2 plus 3 per cent CO_2 respectively on four different subjects in erect posture

Figure 6 represents an experiment carried out on subject F, whose record was shown in figure 2. The only difference between the two experiments is that, while F is standing throughout the whole experiment illustrated in figure 2, he is lying down in the experiment recorded in figure 6. The difference in the reaction of the blood pressure is evident from the comparison of the two records. Equally marked are the differences in the subjective symptoms. Practically all experimental subjects have very little or no complaints whatever during the recumbent position even in those cases where they actually faint or are brought very near to this state in the erect position. As figure 6 indicates, the systolic blood pressure remains practically unaltered. However, a very slight tendency toward a fall is still present in the pure oxygen deficiency experiment and absent in the corresponding experiment with 3 per cent CO_2 . The experiments carried out with other subjects in recumbent position are very similar and, therefore, omitted. The results justify the statement that characteristic differences in blood pressure occur during oxygen deficiency with and without 3 per

cent CO_2 in the erect position of the experimental subjects, whereas in the recumbent position no such differences in blood pressure exist

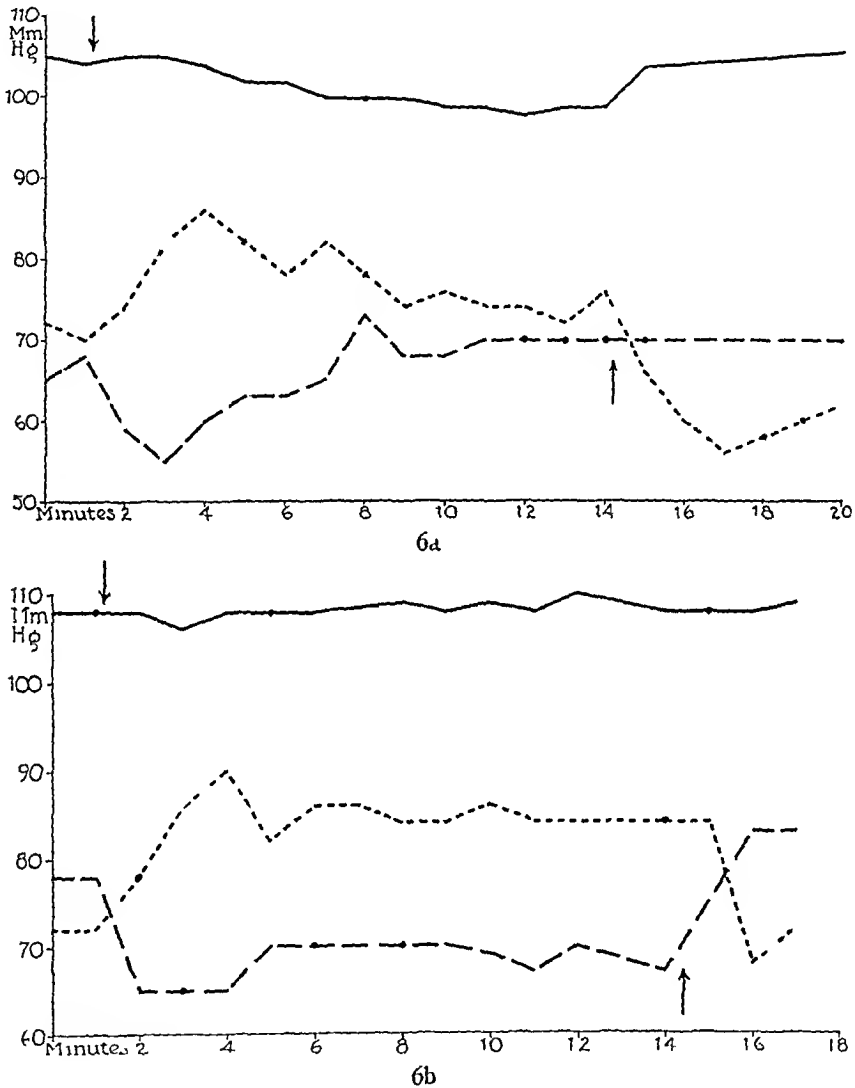


FIG 6a and 6b 85 per cent O_2 and 85 per cent O_2 plus 3 per cent CO_2 respectively between arrows (Subject Fa, lying down)

DISCUSSION

The first question to be answered is the rôle of acapnia in the differences existing in the oxygen deficiency experiments with and without the presence of 3 per cent CO_2 . It is, of course, clear that in the absence of CO_2 the increased respiration resulting from O_2 want leads to a certain degree of acapnia, and it is known, from numerous papers of Henderson,¹³ that under the influence of acapnia the venous return to the heart is diminished and that, consequently, the systolic blood pressure decreases. The question is to decide what importance must be attributed to this factor under the conditions

of our experiments. Therefore a series of experiments was performed in which the experimental subjects voluntarily increased their respiratory volume to a degree similar to that observed under conditions of O_2 want. As table 1 indicates, the greatest drop in blood pressure observed under these

TABLE I
Maximal Decrease in Blood Pressure in the Erect Position

<i>A</i> Under O_2 Want			
Ste	132	116	—12%
Hei	109	88	—19%
Jen	108	82	—24%
Lam	108	96	—11%
Gol	114	90	—21%
			Average — 17.4%
<i>B</i> Under the Influence of a Hyperpnea Similar to That Occurring in O_2 Want			
Ste	122	112	—8%
Hei	119	114	—4%
Jen	109	107	—2%
Lam	106	102	—4%
Gol	106	104	—2%
			Average — 4%

conditions is negligible in comparison to the decrease in blood pressure present in our O_2 want experiments. It may, therefore, be said that a certain degree of acapnia may have almost no effect on the systolic blood pressure when the oxygenation of the blood remains normal. If, however, oxygen deficiency and acapnia are combined, as was the case in the main experiments described in this paper, the reduction in blood supply to the brain, resulting from the acapnia (Cobb and Fremont-Smith,⁹ Schmidt²⁴), aggravates the condition of anoxemia in the central nervous system to such a degree that the blood pressure falls, particularly when the erect posture favors anoxemia of the brain.

Although we believe, as will be shown later, that the major rôle in the decrease of blood pressure observed under conditions of O_2 want in erect posture is played by the carotid sinus, it is to be expected that the vasomotor center as such is of considerable importance. If this is the case the results mean that the loss of CO_2 interferes with the maintenance of the normal tonus of the vasomotor center more under the conditions of anoxemia than under conditions of normal oxygenation of the central nervous system. This implies that CO_2 increases the blood pressure more in anoxemia than under control conditions. This inference has been tested directly in dogs in as yet unpublished experiments (Gellhorn and Lambert¹¹) and shown to be true. Carbon dioxide increases considerably the blood pressure in dogs which are subjected to O_2 want, although the same concentration of CO_2 may not have any effect on the blood pressure as long as the dog is breathing air.

What then is the final mechanism of the difference in blood pressure under conditions of O_2 want in the absence and in the presence of 3 per cent CO_2 ? Since the blood pressure records show no significant differences in the two conditions in a recumbent position, it must be inferred that the main

factor producing these differences is elicited by the erect posture. Now we know that if we change from the recumbent to the erect position there is a temporary decrease in blood pressure in the carotid artery. This, in turn, brings about a restoration in the blood pressure due to the carotid sinus (and aortic nerves) reflexes. It seems, therefore, that under the conditions of anoxemia these reflexes do not function satisfactorily and that CO_2 is a very potent factor to restore them to normality.

The syndrome which we have observed is similar to that of orthostatic hypotension. Here too the change from the recumbent to the erect posture leads to a very considerable drop in blood pressure. The investigations of Alvarez and Roth (1935) have shown that the efferent path of the sympathetic seems to be somewhat affected, at least in one of the cases studied, and this could at least partially account for the decrease in blood pressure in the erect position. The authors, however, feel that these changes are not sufficient to account for the complete syndrome and mention the possibility "that in this disease of orthostatic hypotension there is some defect in the blood pressure regulating mechanism situated in the carotid sinus, but as yet there is no information on that point." The importance of this mechanism is apparent from clinical observations on hypersensitivity of the carotid sinus when under the influence of mechanical stimulation of the carotid sinus a decrease in systolic blood pressure occurs (Smith²⁵). On the basis of these observations and of our own findings, we think it very probable that the carotid sinus mechanism is deficient under O_2 want, due to an insufficient oxygenation of the centers involved, and that the restoration of the circulation in the presence of CO_2 restores these reflexes sufficiently to prevent a fall in blood pressure.

These considerations make it very probable that the carotid sinus (and possibly the aortic nerves) are of primary importance in the explanation of the blood pressure differences observed under conditions of O_2 want with and without CO_2 in the erect position. But we do not believe that this mechanism explains completely all the subjective and objective differences under the two conditions, since characteristic differences remain, at least to a certain extent, even in the recumbent position. In spite of the fact that a certain degree of O_2 want in the erect posture may produce severe headache, weakness, dizziness, a feeling of fullness of the head, paresthesia, impaired vision and hearing and occasionally nausea, it may cause practically no symptoms in the reclining position whether CO_2 is present or not. Not infrequently, however, cases are observed in which the same degree of O_2 want does produce symptoms of slight dizziness, feeling of warmth and disturbances of special senses (the objects in the room appear darker or purplish, the hearing is slightly impaired) in the recumbent position whereas no symptoms may be elicited in the added presence of 3 per cent CO_2 . This difference is, of course, due to the fact that 3 per cent CO_2 improves the oxygenation of the tissues in general and of the brain in particular. It does so by

- 1 An increase in the respiratory volume
- 2 The right shift in the oxygen dissociation curve (Barcroft³)
- 3 The improved venous return due to the increased muscular tonus (Henderson, Oughterson, Greenberg and Seattle¹⁴)
- 4 The specific effect of CO₂ on the blood vessels of the brain (dilatation), (Cobb and collaborators^{8, 12, 19})
- 5 The increased sensitivity of the vasomotor center to CO₂ under conditions of oxygen want (Gellhorn and Lambert¹¹)

SUMMARY

The influence of O₂ want (8 to 8.5 per cent O₂) with and without 3 per cent CO₂ has been studied in the human in the erect and recumbent positions with respect to blood pressure and pulse rate. The results are as follows:

1 In the recumbent position there are practically no differences between the periods of O₂ want and O₂ want plus 3 per cent CO₂. The blood pressure remains unchanged. The pulse rate is slightly increased in either case.

2 In periods of O₂ want the systolic blood pressure shows, in the erect position, a temporary rise which is followed by a fall below the control values. This fall may lead eventually to collapse. In the presence of CO₂ this is prevented and the systolic blood pressure remains elevated throughout the whole period of O₂ want.

3 The changes in diastolic blood pressure are not constant. The pulse rate shows great variability, in most subjects it follows the blood pressure changes. Collapse may, however, occur even during periods of maximally increased pulse rate.

4 The subjective symptoms of anoxemia are more severe in the erect than in the recumbent position. CO₂ may, in either position, completely prevent, or at least greatly diminish, the occurrence of anoxic symptoms.

5 The aggravation in subjective and objective signs of anoxemia, if the experiment is carried out in the erect position, is thought to be due to the failure of the carotid sinus reflexes under the conditions of oxygen deficiency. The addition of 3 per cent CO₂ to the O₂ deficient gas mixtures under these conditions seems to exert its beneficial effect on the objective and subjective signs by improving the oxygenation of the medullary centers and thereby restoring the carotid sinus reflexes to normal.

6 The effect of a certain degree of acapnia on blood pressure is much greater under anoxic than under normal conditions.

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DEATH COMPLICATING THE WITHDRAWAL OF NARCOTICS, WITH RESPIRATORY DIFFI- CULTIES PREDOMINANT. REPORT OF THREE CASES¹

By PHILIP PIKFR,² M D, and JULES GELPERIN, B M,
Cincinnati, Ohio

DURING the past three years we have seen three dramatic deaths in narcotic addicts who had been suddenly deprived of the drugs to which they had become habituated

A search through the literature for descriptions of and explanations for such occurrences has been singularly unproductive³. In writing on the subject of morphine withdrawal, many authors have commented on the possibility of collapse, particularly as a complication of sudden withdrawal. Their comments, however, have been uniformly casual and incidental, and in no instance have we been able to discover a specific case report. Several general descriptions of the symptoms likely to occur in such collapse were noted, but here again the literature proved disappointing, since none of these brief general references to the manner of death in this type of case mentioned the occurrence of any outstanding respiratory symptom and since practically all of them spoke chiefly of circulatory collapse. It is because of an unusual finding in connection with the respiration in all three of our cases, the absence of circulatory collapse except just before death, and the scarcity of reported detailed material regarding such cases, that this report is being made. On the occasions when our cases were under observation, we had no thought of publishing data concerning them, so that the laboratory investigations were not as numerous as they otherwise might have been. Only one of the cases was studied in some detail. We submit this report with the hope that interest in the subject will be stimulated, and that more information regarding it will be forthcoming.

CASE REPORTS

Case 1 F H, white male, aged 44, admitted May 7, 1936. The patient had been in the hospital on three previous occasions, the first time in order to break the morphine habit, the next two times to be "cured" of paregoric addiction. In each instance sudden withdrawal was accomplished in a thoroughly satisfactory manner.

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² Personal communications from Hans Schwarz of Berlin, Germany, and Manfred Sakel of Vienna, Austria, inform us that those investigators, despite much contact with the subject of morphinism, know of no pertinent information regarding sudden death in this connection, either from their own clinical observation or their acquaintanceship with the literature. We would also like to acknowledge the assistance of Dr. Fritz Moellenhoff, whose knowledge of the foreign literature on the subject was of much help in surveying the field of available information.

with the aid of insulin and ordinary sedatives. Previous to the hospitalization under discussion he had been taking large quantities of paregoric regularly for almost a year. During the two weeks previous to admission, in anticipation of another "cure," he had diminished his paregoric ingestion to two to three ounces per day, and in addition, he had obtained 10 to 15 units of insulin three times per day from his private physician during this two week period.

He was admitted to the ward at 7:30 p.m., walking. He had no subjective complaints other than of a feeling of mild apprehension. He had had his last dose of paregoric at about noon of the day of admission. Physical examination revealed no significant findings except for moderate malnutrition. He was given 15 units of insulin one hour after admission, and 3 drams of paraldehyde one hour later, shortly after which he fell asleep. His sleep, checked at half-hour intervals, was normal until 2:30 a.m.—seven hours after admission, and about 18 hours after his last dose of paregoric. At this time he was found in coma. The significant findings were as follows:

Physical. Temperature 102° F, pulse 80, respiration 48. Respiration peculiar (described under Comment). Pupils dilated and fixed to light. Pulse regular, of good quality. Pulmonary edema. Generalized cyanosis. Blood pressure normal. No significant neurologic findings, save those that would be expected in profound coma. No response to painful or other stimuli. The pulmonary edema responded to atropine.

Urine. Clear amber, sp. gr. 1.030, albumin negative, sugar negative, acetone mildly positive. Microscopic examination negative. *Blood.* Wassermann test negative. Red blood cells 3,900,000, hemoglobin 85 per cent, white blood cells (24 hours after onset of coma) 32,000, with 84 per cent polymorphonuclear leukocytes, 2 per cent lymphocytes, 1 per cent monocytes, and 13 per cent metamyelocytes. CO_2 combining power—16 vol. per cent (4 hours after onset of coma). Urea nitrogen, 21 mg. per cent (4 hours after onset of coma). Sugar, 235 mg. per cent (two hours after intravenous glucose). Phosphorus 2.5 mg. per cent. Chlorides 490 mg. per cent. Non-protein nitrogen 25.6 mg. per cent.

Spinal fluid. Clear, colorless, moderately increased pressure. Globulin normal. Cells normal. Sugar 110 mg. per cent (2 hours after intravenous glucose). Chlorides 750 mg. per cent. Wassermann test negative.

Roentgen-ray of chest (19 hours after onset of coma) negative.

The medications used during the coma were hypertonic glucose intravenously and by hypodermoclysis, physiologic saline by hypodermoclysis, intravenous and intramuscular calcium gluconate, subcutaneous atropine sulphate, caffeine sodium benzoate, and insulin, and intravenous and intramuscular aminophyllin. Morphine was started seven hours after the onset of coma and given in 1/4 to 1/6 grain doses every four hours thereafter, without effect.

Course. The patient remained in coma until death intervened on May 10, 1936. His temperature rose steadily to 107° F, and his pulse rate to 160+. His respiratory rate fluctuated between 30 and 48 per minute. On the second day of the coma he had a generalized convulsion lasting five minutes. Bronchopneumonia was noted several hours before death occurred, and circulatory collapse manifested itself during the last few hours.

Autopsy. Gross findings were lobular pneumonia, toxic changes and chronic passive congestion of the viscera, aortic atherosclerosis, possible early coronary sclerosis, early fatty infiltration of the liver, and cerebral congestion and edema. Microscopic findings were lobular pneumonia, toxic changes in the viscera, early generalized arterio and arteriolar sclerosis, heart negative except for toxic myocardosis, focal necrosis and fatty infiltration of the liver, chronic prostatitis with hyperplasia, cerebral congestion and edema, chronic leptomeningitis, and early degenerative changes in the pons.

Case 2 M H, white male, aged 36 The patient had been taking 18 grains of morphine intravenously per day During the week previous to admission to the hospital, he had been drinking excessively, and had not been able to obtain any narcotics His condition suggested an impending delirium tremens for the first two days in the hospital, and he manifested no symptoms that might have been interpreted as specifically due to withdrawal of narcotics Two days after admission he was found in deep coma and breathing peculiarly Physical examination revealed generalized cyanosis, pulmonary edema, marked generalized muscular irritability, and fixed dilated pupils No other significant physical or neurologic findings were noted The circulation seemed adequate Only ordinary delirium tremens treatment (spinal fluid drainage, dehydrants, fluids, caffeine, and ordinary sedatives) had been used previous to the onset of coma Thereafter, atropine was given as indicated for the pulmonary edema, insulin and intravenous hypertonic glucose were used irregularly, and morphine was administered every four hours Both the coma and the unorthodox respiration fluctuated irregularly, and seemed to bear no relation to the medications administered Morphine apparently had no effect The patient was frequently delirious between comatose periods, and had numerous generalized convulsions The basic neurologic picture did not change The temperature rose to 106° F, the pulse to 150, and the respiration to 52, two days after the onset of the coma, thereafter all three subsided to close to normal for a day, and then steadily mounted, the temperature to 108°, the pulse to 160+, and the respirations to 64 At this time, six days after the onset of coma, evidences of terminal bronchopneumonia and circulatory collapse were observed and were followed shortly by the patient's death The blood and spinal fluid tests gave no evidence of syphilis An autopsy was not performed

Case 3 E P, a white male, aged 49, had been taking 1½ grains of heroin intravenously per day He took his last dose three days prior to hospitalization On admission at 12 30 a m he was found to be in good physical and mental condition, and complained only of cramp-like pains in the abdomen He was given paraldehyde, and soon was sleeping peacefully At 3 30 a m (three hours after admission) his unusual respiration was noted, and he could not be aroused Stimulants were given without effect No other medications were given during the patient's stay in the hospital Morphine was not administered He died two hours after the onset of coma Autopsy was not done No further details were reported on the patient's record

COMMENT

In the cases reported, the outstanding clinical manifestations common to all three were coma, an unusual respiratory disturbance and death We would like to call attention again to the respiratory phenomenon, for which we can offer no explanation The respiration was irregular in rhythm and uniformly deep Periods of apnea of varying lengths (up to 1½ minutes) occurred at irregular intervals, to be followed immediately by deep, gasping inspirations during which all the accessory muscles of respiration were put to vigorous use The expiratory phases were not particularly forceful Generalized cyanosis was quite marked These dyspneic periods fluctuated in duration in the same patient, lasting from five minutes to several hours During the intervals between the attacks of dyspnea, which also varied in length, the cyanosis diminished The administration of morphine sulphate subcutaneously had no appreciable effect It was thought that subcutaneous caffeine-sodium-benzoate occasionally lessened the respiratory distress for

short periods. Though the respiration suggested the Cheyne-Stokes type of breathing in some respects, it was by no means typical. All the clinicians who observed these cases agreed that the respiratory difficulty was almost certainly central in origin. Gross and histologic study of the medulla on postmortem examination of the only one of these cases that came to the autopsy table revealed no enlightening pathology. Whether the degenerative changes present in the pons offered a significant clue was not clear to us. It is known that the depressing effect of a poisonous dose of morphine on the respiratory center of the frog will eventually result in a type of respiration which is somewhat like that seen in our patients. This fact, however, does not explain why abrupt withdrawal of the poisonous substance should produce a similar result.

Another aspect of the problem which has seemed to us to be worthy of emphasis is the fact that the unusual respiratory behavior was common to the three cases despite the existence in each case of factors which made it distinct from the others. The type of opium derivative to which each was habituated, the time between the patient's last dose of drug and the onset of coma and respiratory difficulty, the non-narcotic medication given before and after the onset of the coma—these and other factors varied markedly in the three cases. To us these differences served to make the common findings stand out even more prominently.

We would also like to point out that the circulatory failure so frequently mentioned in the general discussions in the literature as being an outstanding manifestation of the collapse of narcotic withdrawal, did not occur in those two of our patients concerning whom we have adequate information recorded (save as a terminal phenomenon).

Finally we would like to stress that, contrary to a notion that seems to prevail among many clinicians, withdrawal of narcotics from addicts may be complicated by death sufficiently frequently to indicate first, the need for considerable care in the selection of cases for withdrawal and of the choice of method of withdrawal for individual patients, and second, the necessity for diligent clinical observation of patients during the course of withdrawal.

SUMMARY

- 1 Three cases are presented, in which death complicated the sudden withdrawal of narcotics from addicts (*morphine*)
- 2 An unusual respiratory disturbance, common to the three cases, is described (*central type*)
- 3 The absence of circulatory collapse in these cases is pointed out

FATAL IODINE POISONING A CLINICO-PATHOLOGIC AND EXPERIMENTAL STUDY

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It is noteworthy that although iodine is used so extensively, comparatively few cases of death through its use have been reported in the medical literature. American medical literature, in particular, contains very few references to either fatal or non-fatal iodine poisoning.

Up to 1911 Witthause¹ found in the literature only 31 cases of poisoning by iodine. Reports from the Westend Hospital in Berlin show that during the years 1912 to 1925, of 1838 cases of poisoning only one instance of iodine poisoning is recorded, the patient recovering.² Non-fatal iodine poisoning following the oral administration of iodine-containing dye for gall-bladder visualization has been recently reported by Davis and Ross.³ A remarkable case of iodine poisoning with recovery is described by Lejbowsch.⁴

The symptoms of acute iodine poisoning are varied. According to Webster,⁵ the local application of an iodine preparation results in a brownish discoloration of the skin with a desquamative dermatitis which may become purulent. When taken internally, the mucous membranes of the mouth, esophagus and stomach are colored brown. The patient vomits a fluid which is usually brownish, but which is colored blue if the stomach contains starches or if the patient is given starch water as an antidote. The bowels move frequently, passing liquid stools, occasionally with mucus. The pulse becomes weak, urinary retention generally results. In fatal cases anuria develops, followed by delirium, stupor and finally collapse.

Bastedo⁶ describes an iodide fever which may develop even after the local application of an iodine ointment. A few deaths due to the therapeutic use of iodine have been reported.^{7, 8, 9}

Numerous instances of poisoning have occurred due to mistakes in accidentally substituting iodine for other darkly colored medicine. Usually the mistake is noticed immediately and prompt action usually averts a fatal ending.

Suicidal intent is responsible for most of the fatal iodine poisonings. With suicide in mind the individual usually takes a tremendous dose, or else delays calling for help sufficiently long for treatment to be of no avail.

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From the above reports it is apparent that deaths from iodine poisoning fall into three groups

Group I Medicinal use, internally, by injection or by local application

Group II Ingestion of iodine by mistaking it for another drug

Group III Ingestion with suicidal intent

Studying the records of the Medical Examiner's Office of New York City for the past six years, we found 18 instances of suicide by iodine. Of these cases, 13 were males and five females. Death occurred usually within 48 hours after taking the iodine solution. In two instances death resulted within one-half hour and one hour respectively. One individual died after 52 days, following an operation for stenosis of the esophagus which resulted from the ingestion of the iodine. The amount taken, recorded in only nine cases, varied between one and eight ounces of the tincture.

All 18 cases came to necropsy. A number of anatomical diagnoses were made in each instance but the principal causes of death were as follows

Pneumonia	six cases
Pulmonary edema	three cases
Cardiac failure	three cases
Asphyxiation	one case
Peritonitis	one case
Acute corrosive gastritis	one case
Acute ulcerative colitis	one case
Acute parenchymatous degeneration of the liver	one case

In one case the direct cause of death could not be determined because of the condition of the body.

Of the few cases reported in the literature, edema of the glottis is mentioned frequently as the cause of death. One patient was saved by a prompt tracheotomy.¹⁰ In our series of 18 patients only one died as a result of asphyxiation.

In four cases no tests for iodine were made. In two cases in which no iodine was found either in the stomach contents or in the liver, one patient had died 12 hours and the other 52 days after the ingestion of iodine. In the remaining cases, iodine was found in the stomach alone six times, in the liver alone twice, in the stomach and liver twice, in the stomach, liver and kidneys once, and in the jejunal contents and liver once. In this case (number 10) an old gastro-jejunostomy opening was found. Of the two cases in which iodine was found in the liver and not in the stomach contents one had died after 49 hours (number 14), the other (number 8), after 61 hours.

Not all of the above cases presented similar pathologic changes. Iodine is a cell poison, although the slowest acting of the halogen group. Because iodine combines readily with starches, proteins and unsaturated fatty acids forming stable combinations, much of the ingested iodine may become bound to any of these food substances present in the stomach. Since such compounds are but poorly and slowly dissociated their toxic effects are lessened or the drug rendered totally inactive. The minimum lethal dose

(in man is not known. Death has been caused by 20 grams of iodine, and recovery has followed the taking of 150 grams¹¹

Table 1 gives a resumé of the chief anatomical findings of the 18 cases found in the Medical Examiner's Office. As far as could be ascertained from the protocols the extent of the pathologic changes in the organs bore no relation to the length of time between the ingestion of the drug and death. It will be noted that in all but four cases (numbers 6, 7, 9 and 18) the stomach mucosa was affected, the degree of change varying from simple staining to complete necrosis and edema of the wall. In no instance was there any perforation, although in one case (number 8) the stomach wall was noted as abnormally thinned. In those cases in which the amount of ingested iodine was determinable, there was no parallelism between the amount ingested and the degree of gastric involvement, nor was there any apparent parallel between this and the amount of iodine found in the gastric contents, either as free iodine or in combined form (see case 18). The duodenum was involved 11 times, the degree varying from congestion to widespread mucosal necrosis. As with the stomach, there was no apparent correlation with the amount of iodine ingested. It will, however, be noted that, with the exception of case 14 in which four days elapsed before death, the duodenum was involved only in those cases wherein death ensued within a few hours after the ingestion of the drug. The small intestine showed mucosal involvement in only three instances, while the colon showed ulceration of the mucosa only in the case of a patient who had lived for five days after taking the iodine. In view of the fact, however, that two other patients in this series survived for longer periods and showed no such colonic lesion this case must be considered exceptional, especially since no similar finding has been recorded in the literature.

The liver showed gross changes in 14 instances. In five cases there was congestion alone, in six gross fatty changes, in four marked cloudy swelling. Histologic examination was available only in our own case (*vide infra*) in which extensive fatty changes were noted. As with the stomach, the amount of iodine or iodide in the liver could not be correlated with the changes noted. Thus, in case 14, 11.5 mg. of iodine were found in 1000 gm. of a liver that grossly showed fatty changes, while in case 10, with 86 mg. of iodine in 500 gm., the liver was merely congested. In this series of cases, there were apparently no gross changes in the gall-bladders, nor do we find any record of clinical determinations for iodine in gall-bladder bile. That these findings may have been complicated by the treatment given the patient is suggested by case 3. In this case a definite history of iodine ingestion was obtained. At autopsy a severe corrosive gastritis and esophagitis was found, one of the most severe in the entire series, coupled with marked cloudy swelling of the liver. Detailed chemical studies of these viscera failed, however, to reveal any trace of free or combined iodine, or other poison, and it was later learned that repeated intensive

TABLE I
Summary of Gross Pathological Changes Observed in 18 Autopsied Cases Found in Medical Examiner's Office

Case No	Duration of Life	Amt Iodine Ingested	Gross Pathological Changes Observed in								Weight of kidneys	Iodine Found
			Lungs	Stomach	Duodenum	Small Intestines	Colon	Liver	Gall Bladder	Kidneys		
1	12 days	Un known	Discrete hemorrhages lower half	Mucous membrane dark hemorrhage	Not noted	Not noted	None	None	None	Cortex pale	500 gm	Not examined
2	10 hours	6 ounces	Mucous membrane stained dark brown flaky and strand like desquamation near cardia	Scattered hemorrhages in smooth mucous membrane with absent rugae	None	None	None	None	None	Cortex pale smooth	300 gm	None in liver kidney stomach contents
3	13 hours	Un known	Shale gray, dry cooked mucous membrane swollen with Mucous membrane easily separable	Gray blue cooked mucous membrane easily separable, eroded near incisura	Mucous membrane patchy blue gray, submucosal vessels thrombosed	As for duodenum	None	Glazed markings not distinguished	None	Congested	205 gm	None in brain liver kidney stomach contents
4	Few hours	3 ounces	Mucous membrane white easily separable dry cooked membrane	Mucous membrane extensively corroded esp along lesser curvature, light gray granular easily separable membrane	Gray friable mucous membrane	As for duodenum	None	Congested markings indistinct	None	Congested	Normal	Large amounts combined iodine (iodide) in gastric contents no free iodine other organs not examined
5	Few hours	Un known	Not noted	Edematous, congested wall, mucous membrane thickened gray black	Patchy necrosis of mucous membrane with extensive intramucosal hemorrhages	None	None	Flabby fatty markings indistinct	None	Markedly congested	200 gm	Not examined
6	52 days	Un known	See detailed report in text	None	None	None	None	Fatty	None	Congested	370 gm	Not examined
7	38 hours	3 ounces	Not noted	None	Not noted	Not noted	Not noted	Normal	None	Pale cortex markings indistinct	Normal	No iodine or iodide in liver and kidney
8	2 days	3 ounces	Mucous membrane largely necrotic, well reddened thinned	Mucous membrane necrotic yellow brown especially along lesser curvature, wall markedly thinned	None	None	None	Fatty	None	Pale cortex	360 gm	Early large amount of iodide in liver
9	5 days	1 ounce	Not noted	Normal mucous membrane and wall	None	None	Ulcerative colitis	Glassy fatty	None	Pale edematous	Somewhat enlarged	Not examined

TABLE I—Continued

Case No	Duration of Life	Amt Iodine Ingested	Gross Pathological Changes Observed in							Weight of Kidneys	Iodine Found
			Esophagus	Stomach	Duodenum	Small Intestines	Colon	Liver	Gall-Bladder		
10	4 hours	Un known	None	Submucosal hemorrhages	Terminal duodenum and adjacent 4 ft. of jejunum acutely inflamed, mucous membrane covered by extensive gray friable separable membrane. Case had had antecedent partial gastrectomy	None	None	Congested markings indistinct	None	Not noted	Liver 86 mg iodine in 500 gm tissue Jejunum contents 122 mg free iodine in 20 c c
11	Un known	Evidently 8 ounces	None	Corroded mucous membrane	Autolytic mucous membrane	None	None	Autolytic	Autolytic	Not noted	Liver 31.5 mg iodine in 500 gm tissue Kidney 5.6 mg iodine in 100 gm tissue Stomach 156 mg iodine in total Not examined
12	1 to 1½ hours	Un known	Not noted	Mucous membrane necrotic throughout	Congested	None	None	Congested markings indistinct	None	Not noted	Absent in kidney
13	2 days	1 ounce	Not noted	Mucous membrane stained brown throughout, occasional petechial hemorrhage	Not noted	Not noted	None	Congested markings indistinct	None	Not noted	
14	4 days	2 ounces	Mucous membrane pitchily eroded	Mucous membrane markedly swollen hemorrhagic	Congested	None	None	Congested fatty	None	In large	Liver 21.5 mg iodine in 500 gm tissue
15	3 hours	Un known	Not noted	Mucous membrane gray brown soft not eroded	Congested	None	None	Congested	None	Not noted	Free iodine present in fairly large amounts in gastric contents Iodides present in fair amounts in liver
16	1 hour	¼ pint	Not noted	Mucous membrane caked uniformly brown red	As in stomach	None	None	Congested	None	Not noted	Large amounts free iodine in gastric contents
17	2 hours	Un known	Not noted	Mucous membrane thick, gray parched patchily blackened and eroded	Markedly congested	Mucous membrane of upper jejunum markedly congested	None	Fatty	None	Normal	Large amounts free iodine in gastric contents
18	7 hours	Un known	Not noted	Normal	Mucous membrane stained brown contains small amount of blood	None	None	Fatty	None	Normal	Iodide 24.4 mg in gastric contents 11.5 mg in 1000 gm liver tissue

lavage of the stomach with starch and milk had been performed early in the treatment

In all but three instances the kidneys showed pallor, congestion, or indistinct markings. In two instances the cortex was noted as swollen, in one as indistinguishable from the medulla. Here again neither the amount of iodine ingested nor that found in the kidney nor the time interval between ingestion and death could be correlated with the gross anatomical findings. Histologic examination was done only in case 2, in which there was found intense congestion of the interstitial capillaries, and red cells and red cell casts in the collecting tubules. There was intense, but rather patchy, congestion of the glomerular capillaries, this contrasts with the findings in our own case in which the glomeruli were chiefly bloodless and their lumina apparently occluded by the swollen endothelial cells in apposition. This apparent morphological difference may be due to the difference in the length of life after the iodine ingestion. The longer duration in our case may have accounted for the reactive cellular changes observed in the glomeruli, the ischemia being due to the mechanical occlusion of the lumina by the swollen cells in apposition—a change obviously requiring more than the few hours interval present in case 2. In neither instance were there gross changes suggesting an acute diffuse glomerulo-nephritis or isolated glomerulitis nor was there histologically any increase in endothelial, epithelial or interstitial cells, no thickening of the basement membrane, nor any evidence of inflammation.

With material such as ours, dependent as it necessarily is on clinical reports from a number of institutions—which are never detailed and are frequently confined to a mere statement of the fact of iodine ingestion and its apparent intent—any analysis of symptoms is not entirely satisfactory. Nevertheless, anuria appears in the records twice (cases 1 and 9) and a clinical diagnosis of uremia once (case 9). These two cases are among those of longest duration in the series, respectively twelve and five days.

Because of the incompleteness of the data, an attempt was made to determine experimentally the effects of iodine on the kidneys. Two rabbits were given respectively 5 c c and 3 c c of tincture of iodine intravenously. The first rapidly went into shock and died in four hours. At autopsy no gross or histologic renal changes were apparent except for marked congestion of the glomerular and interstitial capillaries and a slight degree of cloudy swelling of the convoluted tubular epithelium. The liver showed moderate cloudy swelling, the cardiac muscle fibers were markedly swollen, the striations indistinct and markedly fragmented. The gastric mucosa was reddened but not eroded.

The second rabbit lived 24 hours. At autopsy, the renal, cardiac and hepatic findings, both grossly and microscopically, were identical with those noted in the first rabbit. The gastric mucosa of the pyloric half of the stomach showed a widespread ulceration and brownish discoloration of the

mucosa The ulcer was shallow and covered by a friable, necrotic brownish membrane which, when separated, revealed the ulcer base formed by the reddened muscularis Its edges were formed by reddened, edematous mucosa which was easily separable from the gastric wall On section, the ulcer was covered by necrotic mucosa and a leukocytic debris In the superficial layer of the muscularis were thrombosed veins with necrotic walls Chemical examination of the gastric contents revealed iodine in organic combination

Two other fasting rabbits were given 5 c c of tincture of iodine by nasal catheter (under fluoroscopic guidance) intragastrically These exhibited no untoward symptoms and lived for one week and 10 days respectively At autopsy, mucosal necrosis of the gastric fundus near the pylorus was noted in each rabbit as well as of the adjacent duodenum No gross or histologic renal changes were present The liver showed marked and widespread fat phanerotic changes, involving the greater part of each lobule The heart muscle showed considerable cloudy swelling The urea nitrogen had risen from 16 mg per cent to 41 mg per cent before death

Because of the presence of only moderate congestive glomerular findings, both in the human cases and in the experimental animals, it is doubtful whether the apparent uremia was of renal origin In most cases of iodine ingestion, severe and protracted vomiting or gastric lavages, often repeated, result in the loss of large quantities of electrolytes It is doubtful if any electrolytes taken in solution orally can be absorbed through a mucosa so congested, baked, caked, necrotic, or ulcerated as that usually seen in the stomach and adjacent duodenum and occasionally in the small intestines in cases of iodine ingestion Even in those cases where no gross mucosal involvement is present, the intestines are usually dilated and contain large amount of grumous, gray, turbid, or blackened material These findings resemble those present in paralytic ileus There is no question but what serious loss of electrolytes and water will cause renal suppression with a resulting nitrogen retention, a condition long recognized and treated in cases of intestinal obstruction It is further a matter of everyday clinical experience that such a state occurs more rapidly the higher the obstruction In cases of iodine poisoning the pathologic changes are usually in the stomach, duodenum and upper intestine

It has also been shown that urinary suppression and a rise in blood nitrogen can be produced by forced diuresis initiated by repeated injections of sucrose¹² It is possible that glucose acts in a similar manner¹⁸ Yet, in an attempt to spare the liver from damage so frequently present in the cases cited, the intravenous injection of glucose was resorted to in our case, as is usual in clinical practice However, as we have here shown, the kidneys in cases of iodine poisoning already show cloudy swelling and probably increased permeability It can therefore easily be seen how this procedure only increases the dehydration thus further increasing the toxemia It

would be better merely to replace electrolytes by the intravenous route and leave until later in the clinical course the administration of caloric necessities and then by the subcutaneous rather than the intravenous routes. It may even be that the electrolytes and fluids themselves had better be administered subcutaneously as was done by Lejbowitsch.⁴

Of passing interest is the symptom of shock present in 11 of our cases (numbers 1, 2, 4, 5, 10, 12, 13, 15, 16, 17, 18). This may perhaps be associated with the myocardial changes such as were present in our experimental rabbits which were injected intravenously, or this shock may be due to a severe disturbance of the splanchnic nerves due to changes incident to the gastric and duodenal and hepatic lesions.¹⁴

Of interest also is the extremely early development of clinical symptoms and signs of pulmonary parenchymal (pneumonic) involvement, and the pathologic changes even a few hours after the ingestion of the drug. Thus, in case 2 dying about 10 hours after the iodine ingestion, "the trachea and larger bronchi contained a foul smelling, brown material and some yellow creamy pus pouring forth in large quantities from the upper and lower bronchi. The lungs, especially the lower lobes, are irregularly, but widely consolidated, the consolidation being distinctly peribronchial in distribution." In case 3 dying 13 hours after the iodine had been ingested, "the bronchi contained mushy gray purulent contents." It is possible that the gastric necrosis and the vomiting caused more than usual intrabronchial aspiration of gastric contents, and that lavage in the presence of such abnormal peristalsis and the marked relaxation of gastric and bronchial walls allowed of easy ingress of the lavage material into the lungs already the seat of an edema (case 1). No instances are recorded of the presence or absence of bacteria in the gastric contents but it is doubtful whether the ingested tincture of iodine can so rapidly eliminate organisms contained in the stomach.

Case 6 deserves brief individual comment. In this case there was a definite history of the ingestion of iodine with suicidal intent, and the presence of iodine burns of the lips and tongue. With gastric lavage the patient recovered from the acute symptoms, but thereafter gradually but progressively developed symptoms of esophageal obstruction. Esophagoscopy 33 days after the iodine ingestion revealed the mucous membrane just above the cardia to be so scarred as to cause stenosis. After two unsuccessful attempts at dilatation, gastrostomy was performed, the patient dying of a general peritonitis and mediastinitis four days thereafter. At autopsy a transverse puckering of the esophageal mucosa and scarring of the wall were present 3 cm. above the cardiac end of the stomach. The esophageal lumen was so narrowed that a probe 4 mm. in diameter could barely be passed into the stomach. The scarred area involved the entire terminal 3 cm. of esophagus and adjacent 2 cm. of gastric mucosa. The patient lived for 52 days after the ingestion of the drug and hence no chemical analysis for iodine was performed post mortem. However, the history

obtained repeatedly during the patient's lengthy stay in the hospital, as well as analysis of washings from the bottle supposed to have contained the drug ingested, failed utterly to indicate any substances other than iodine. So far as we could ascertain, this is the only recorded case of esophageal stenosis caused by iodine.

CASE REPORT

On May 25, 1935, at about 1 30 p.m., a 29 year old white man was sent to the Beth-El Hospital by Dr. Nathan Davis four days after having taken an unknown amount of tincture of iodine during a period of despondency.

The patient appeared to be fairly well nourished but looked ill. His eyes reacted to light and accommodation, the sclerae were slightly jaundiced. No pathological changes were evident in the nose and throat. Examination of the mouth revealed dry lips and a dry coated tongue with a few ulcerations of the buccal mucosa. The breath presented a peculiar odor.

The expansion of the chest was fair. The respiratory rate was somewhat increased, no râles were heard. The heart was regular in rate and rhythm. The sounds were of good quality and no murmurs were heard. Examination of the abdomen showed some tenderness over the liver region. The rigid recti muscles prevented proper palpation of the liver and spleen. The skin was somewhat cyanotic but no jaundice was noted. The extremities showed no abnormal findings except a slight cyanosis under the nails.

The systolic blood pressure was 140, the diastolic 80, the pulse rate 96 per minute, respiration 24 per minute and the temperature 99.4° F.

On admission to the hospital, five ounces of urine were obtained by catheterization. It was smoky in color, specific gravity 1.010, acid in reaction, albumin 2 plus, glucose negative, and acetone positive, no casts were found, some white and red blood cells and epithelial cells were present. Iodine in organic combination was found in the urine. The blood count showed 5,000,000 red blood cells, 70 per cent hemoglobin, 14,000 white blood cells, with 85 per cent polymorphonuclear neutrophils and 15 per cent lymphocytes. Blood chemistry: glucose 142 mg per cent, urea nitrogen 150 mg per cent, non-protein nitrogen 228 mg per cent, creatinine 7.5 mg per cent, uric acid 5.6 mg per cent, chlorides 556 mg per cent, phosphorus 3.5 mg per cent.

On admission, 250 c.c. of 25 per cent glucose solution were given intravenously and a retention enema of 1000 c.c. of 15 per cent glucose solution and 5 per cent sodium bicarbonate was also given. To rule out a possible gastric perforation a roentgenogram of the abdomen was taken. No evidence of free gas in the abdomen was found. The left kidney appeared larger than the right. There was no evidence of radio-opaque substance in the renal regions.

The first evening after admission the patient vomited a small amount of light brown fluid with bloody mucus, and passed a dark brown liquid stool. That night the patient complained of abdominal soreness. At 11 p.m. the patient was taken to the operating room, 600 c.c. of blood were removed and 450 c.c. of blood were given by direct transfusion. The blood pressure, taken again at this time, was 142 systolic and 60 diastolic. During the remainder of the night, the patient slept very little because of frequent and severe abdominal cramps.

During the second day the patient again complained of severe abdominal pain which was relieved by morphine sulphate. The patient vomited only once during the day. Intravenous injections of 250 c.c. of 25 per cent glucose solution were given during the morning and evening. At midday a solution of 1000 c.c. of normal saline was administered by hypodermoclysis. During the second night, the patient was

restless because of the continued abdominal pain but slept at short intervals. At 11 p.m. another hypodermoclysis of 750 c.c. of normal saline solution was given.

On the third day the jaundice noted in the sclerae on admission had practically disappeared. The abdomen was more distended, some rigidity in the upper right quadrant was noted. Only three ounces of urine were obtained by catheterization. At this time 500 c.c. of blood were again removed and an equal amount of whole blood given by direct transfusion. The patient continued to be restless and slept only at intervals.

On the fourth day 10 c.c. of sodium thiosulphate solution were given intravenously. Anuria developed, colonic irrigations were given with no evident benefit. On the fourth and fifth days the patient continued to be restless but treatment was continued. The blood urea rose to 172 mg. per cent and blood creatinine to 12 mg. per cent. The blood CO_2 was 18 volumes per cent. Sodium bicarbonate in a 5 per cent solution was given intravenously. During the night of the fifth day, the patient became irrational, very noisy and restless. Twitching developed in various parts of the body.

On the sixth day the temperature rose to 104°F , the patient sweated profusely, was still irrational and toward noon sank into coma. General cyanosis developed and the patient died at 6 p.m.

The urine was always dark and smoky, and contained hyaline and granular casts, but no red cells were found on the third day after admission. The temperature on admission was 99.4°F and rose on the third day to 103.2°F fluctuating on the fourth and fifth days and at the close of the fifth day rose to 104.2°F coming down at the time of death on the sixth day to 102°F .

Autopsy Report The body is that of an adult male of about 30 years of age, 62 inches in height, slight in build, weighing about 120 pounds. The pupils are equal and in mid-dilatation. There are no external evidences of injury. On the buccal mucosa just within the lip line several small white ulcerations are present, pinhead to lentil in size. There is no other discoloration of the buccal mucosa, gums or tongue.

The head was not examined.

The thyroid gland is normal in size and shape and weighs 21 grams. On section the gland reveals a finely lobulated appearance and is of a pale brownish red color not unlike skeletal muscle. There is no lymphadenopathy. Nothing unusual is found in the pharyngeal mucosa.

Internally, the esophagus is covered by a thin, friable membrane of a yellowish brown color in its lower third. This membrane strips easily revealing a reddened submucosa. The upper portion of the esophagus is intact.

The pleural cavities contain a small amount of clear yellow fluid. The visceral pleura is reddened and dull but not covered by any exudate.

The lungs are voluminous, heavy, soggy and moderately firm. The firm areas tend to be patchy in arrangement with the intervening areas pale and fluffy. On section the smaller bronchi contain variable quantities of debris (gastric contents). Moderately firm areas varying in size from a lung lobule to a third of the lobe are present and are irregularly distributed throughout the lungs. These areas are drier than the surrounding parenchyma. A definite relationship to the bronchi or vessels is lacking. The cut surfaces ooze large quantities of frothy serosanguinous fluid. The larger bronchi and lower end of the trachea show a red and edematous mucosa but there are no ulcerations or discolorations.

The pericardial cavity contains a few c.c. of clear yellow fluid. The heart is normal in size, shape and configuration. The valves and orifices show no changes. The ventricular muscle is of a deep brownish red color and is unusually soft and flabby. There are no areas of fibrosis or softening. The coronary vessels are soft and pliable.

The peritoneal cavity contains about 1200 cc of clear yellow fluid. The loops of the small bowel are heavy with contained fluid. All peritoneal surfaces are smooth and glistening.

The entire mucosal surface of the stomach is covered with a dirty yellowish membrane which is more pronounced in broad longitudinal streaks (rugae). The membrane strips easily revealing an intensely edematous and congested submucosa. This membrane stops abruptly at the pylorus. The gastric wall is thickened by edema and congestion. There is no exudate on its peritoneal surface. There are no perforations. The duodenum is intensely congested and edematous and stains a deep yellowish brown, but lacks a definite membrane such as is seen in the stomach. The duodenal lesion involves the entire length of the duodenum and a similar but progressively less marked lesion is seen in the first 10 inches of the jejunum (figure 1).

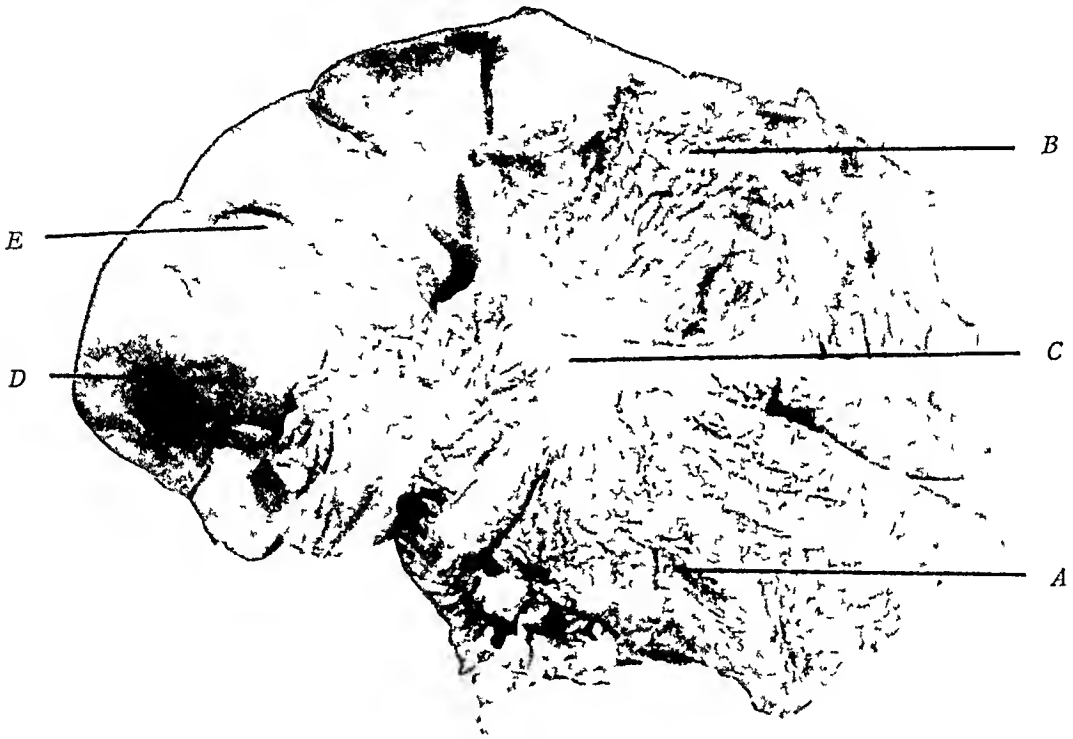


FIG 1 Photograph of fresh liver, stomach and gall-bladder from our own case. The stomach was opened along the greater curvature to show the mucosal surface. Note the widespread necrosis and diphtheritic gastritis at *A*, the necrosis of tops of rugae at *B*, also the relatively intact mucosa of the lesser curvature near the pylorus at *C*. *D* is the liver and *E* the gall-bladder.

The remainder of the small intestine shows distention of the small veins with occasional minute extravasations of blood in the subserosal tissue.

The gall-bladder is markedly distended by an opaque muddy brown liquid of low viscosity. The mucosa of the gall-bladder shows a patchy denudation with ragged edges of mucosa which project into the lumen. The cystic duct, common duct, and hepatic ducts show no changes. The ampulla of Vater is normal.

The capsule of the liver is smooth and glistening. On section the organ shows a nutmeg-like appearance due to a brownish yellow deposit in the periportal region.

The individual lobules are markedly swollen. The general cut surface has a pale yellowish appearance.

The pancreas shows normal lobulation.

The colon is normal. The mucosa and submucosa of the rectum are markedly edematous.

The spleen is large and soft, and weighs 300 grams. The edges and notches are rounded. On section the pulp is everted over the cut edges. The Malpighian bodies are large, hazy and tend to be confluent. The pulp is moderately soft but not diffuent.

The kidneys weigh 160 grams each. The capsules strip easily leaving a smooth surface. On section the cortex is markedly widened and bulges over the cut edges. The cortical markings are hazy. The glomeruli are prominent as pinhead red dots. The medullary markings especially at the cortico-medullary junction are moderately hazy. The pelves and ureters show no abnormalities.

The bladder mucosa is somewhat reddened and edematous. The verumontanum projects into the bladder as a long finger-like structure with a reddened and edematous bulbous ending.

The adrenals show no abnormal findings.

Microscopical Examination. Sections of lung show patchy areas of consolidation distributed throughout all lobes of the lungs with intervening areas of parenchyma showing no changes beyond congestion and intra-alveolar edema. The consolidated portions of the lungs show an intra-alveolar exudate consisting of polymorphonuclear cells, large mononuclear cells and red blood cells and serum. The amount of fibrin in the exudate is minimal. The small bronchioles show complete or partial desquamation of their lining epithelium, their lumens are filled with desquamated epithelial and polymorphonuclear cells. The larger bronchioles show desquamation of the lining epithelium with moderate congestion and leukocytic infiltration of the walls.

Sections of the heart show no changes in the pericardium, myocardium or endocardium. The aorta shows scattered numbers of large mononuclear and wandering cells in the intima. No other unusual changes are noted.

The acini of the thyroid are large, but few are cystic. They are lined by cuboidal epithelial cells and are filled with a fairly homogenous pink colloid material. Many of the acini are smaller in size and contain little or no colloid material. The supporting stroma is moderately increased in amount and contains occasional patchy collections of small round cells.

The liver cells contain numerous fine vacuoles evenly distributed in the cells throughout all parts of the lobules. The cells are not markedly swollen. There are no abnormal cellular infiltrations. The vacuoles are stained bright red with Sudan III, are not stained with Nile-blue sulphate, osmic acid or by the Lorrain-Smith-Dietrich method (vacuoles are fatty acids).

There are no unusual changes in the parenchyma, islands of Langerhans or ducts of the pancreas.

The glomerular loops in the kidney are bloodless. There is, however, no increase in the number of nuclei. In a few glomeruli a slight amorphous intracapsular exudate is found. The cells lining the parietal layer of Bowman's capsule are swollen, occasionally desquamated and tend to be of cuboidal or of low columnar variety. The convoluted tubules show a marked granular cytoplasmic swelling of their lining cells with disintegration of the peripheral half of the cells so that the lumen appears to be markedly widened. Many of the tubules are filled with well preserved or partially disintegrated red blood cells and large quantities of amorphous pigment.

Sections of the spleen show a diffuse reticulum cell hyperplasia and a moderate congestion of the pulp accompanied by small patchy recent hemorrhages into the red pulp.

The stratified squamous epithelium of the esophagus is rigid and tends to break off from the supporting stroma. The superficial layers of epithelium are keratinized. There are no unusual changes in the mucosal layer. The submucosa is moderately edematous and shows in places small focal collections of round cells while immediately beneath the epithelium there is a patchy leukocytic infiltration.

The mucosa of the stomach is almost completely necrotic. Recognizable epithelial cells are present only at the base of the glands. The upper portions of the gastric mucosa are converted into an amorphous eosinophilic mass. The submucosa is intensely congested, edematous and shows numerous lymphatics crowded with polymorphonuclear cells and lymphocytes. The cellular infiltrate extends along the interstitial tissue and vessels through all layers of the stomach including the serosa.

The mucosa of the gall-bladder is edematous. The stroma is markedly infiltrated with polymorphonuclear leukocytes and some lymphocytes. The cellular infiltration extends deeply into the fibro-muscular layer. Occasional lymphatics in the fibrous layer are distended with polymorphonuclear leukocytes.

Sections of the jejunum show necrotic changes in the mucosa with varying degrees of edema and round cell infiltration of the submucosa. The severity of the lesion decreases as the distance from the pylorus increases. Sections of large bowel show no unusual changes.

Sections of skin and subcutaneous tissue show no abnormal changes in the skin or its appendages.

Sections of testicle show all phases of normal spermatogenesis in the seminiferous tubules.

No degenerative changes or loss of the normal striation could be noted in sections of the skeletal muscle.

Chemical examination disclosed large quantities of iodine as inorganic iodine in the liver and kidneys and both as inorganic and organic iodine in the bile. In the bile, tests for iodine were positive only after separation from conjugated proteins.

SUMMARY

1 A case of fatal iodine poisoning, with detailed autopsy findings, is reported. Eighteen other cases are reported from the records of the Medical Examiner's Office of New York City. The infrequency of fatal iodine poisoning is remarked, but it is suggested that the condition is more prevalent than is currently believed.

2 The renal suppression and nitrogen retention occurring during the course of iodine poisoning is discussed. It is suggested that this happening is the result of extrarenal loss of electrolytes and dehydration. No significant renal lesions were found in the human cases or in the animals experimented upon. It is suggested that therapy be aimed at the replacement of electrolytes and water during the acute phase, and that glucose injections or other measures leading to forced diuresis be avoided.

3 The early appearance of shock and aspirational pneumonia are stressed and the possible mechanism discussed.

4 An instance of esophageal scarring and stenosis is recorded, the only one of its kind in the literature.

The authors desire to express their thanks to Dr. Nathan Davis for the earlier clinical data of this case and also to Dr. Thomas Gonzales, Acting Chief Medical Examiner of the City of New York, for permission to report the 18 cases from the Medical Examiner's Office.

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THE GALACTOSE TOLERANCE TEST IN JAUNDICE; A CONSIDERATION OF THE EVIDENCE PERMIT- TING THE MEASUREMENT OF GALACTOSE UTI- LIZATION BY URINARY EXCRETION; SOME SOURCES FOR ERROR IN ITS INTERPRETATION; AND AN ADDITION IN ROUTINE TECHNIC

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IN 1931, in a paper on the study of the metabolism of galactose in the human subject, Shay, Schloss and Bell¹ concluded that this hexose was best suited for testing the carbohydrate function of the liver. In order for the urinary excretion of this sugar, orally administered, to act as a measure of hepatic carbohydrate function, they considered the following among the necessary conditions: (1) that there be no renal threshold for the excretion of galactose, (2) that galactose utilization remain unmodified by the activity of those endocrine glands known to affect glucose metabolism, (3) that galactose be practically unutilizable by all tissues other than the liver.

Because of the bearing that these facts have upon our thesis, it is essential to examine the more recent evidence which may lend support to the above.

Some investigators have questioned the use of a fixed dose of galactose for this test. We cannot subscribe to the opinion of Roe and Schwartzman² that it is necessary to employ a dose of sugar commensurate with body weight. Shay, Schloss and Bell¹ have demonstrated that the utilization of galactose is independent of age, weight, or sex. Harding and Grant³ also prefer the fixed dose of 40 grams. Although a test amount of the sugar varying with the body weight or with the body surface may seem more logical and scientific, these authors believe that such a fluctuating dose will give no greater uniformity of results. This belief is supported by a comparison of the results of Harding and van Nostrand,⁴ who used a fixed dose of 50 grams, with those of Roe and Schwartzman⁵ who employed a regulated dose of 1 gram per kilogram of body weight. The urinary excretion of both groups will be seen to show large fluctuations. More recently R. K. Owen,⁶ studying a group of 30 normal subjects (15 male, 15 female) between the ages of 20 and 70, found, after a uniform 40 gram dose, a urinary excretion whose variation and average were similar to those found in the normal group studied by Shay, Schloss and Bell¹.

The improvement in the chemical methods for the measurement of small amounts of galactose in the blood has given rise to the feeling that the

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blood galactose curve may be a better measure of galactose utilization than urinary excretion. This would be true if a renal threshold for galactose could be demonstrated. However, the most convincing evidence is against the existence of such a threshold. Fohn and Berglund⁷ first furnished adequate evidence of its absence. They found that very small doses of galactose produced an increase of urinary reducing substances. Later Goldblatt,⁸ studying the blood sugar after galactose administration, observed urinary excretion of galactose in the absence of any rise in blood sugar. Harding and Grant,³ from studies on arterial blood galactose, were convinced that galactosuria can occur with very little rise in blood galactose.

In the absence of a kidney threshold, the blood level of this sugar, so far as the galactose tolerance test is concerned, is of academic interest only. None of the advocates of blood galactose estimations has thus far demonstrated that these are more significant than the measurement of the urinary excretion of this substance in the application of this test to the differential diagnosis of jaundice. We can, therefore, see no reason for converting a valuable laboratory test from a simple office procedure into one almost prohibitive for routine clinical use.

Any liver function test dependent upon the utilization of a sugar must of necessity take into consideration the possible conversion of the test substance in tissues other than the liver. In 1922, Mann and Magath,⁹ while studying the ability of various sugars to combat the hypoglycemia following liver extirpation in the dog, found that injected galactose failed to give any appreciable result. In 1931, Shay, Schloss and Bell¹ demonstrated that in the human subject, after ingestion of galactose, the injection of amounts of insulin capable of producing hypoglycemic blood levels with marked symptoms of hypoglycemia, failed to modify materially the urinary excretion of galactose. Roe and Schwartzman⁵ in 1932 recorded similar results from experiments on dogs.

Following the injection of adrenalin chloride after galactose administration, one of us (H. S.)¹ found a greater output of reducing substances in the urine than had occurred without the adrenalin. However, differential fermentation showed that the extra reducing substances were fermentable, the non-fermentable fraction remaining similar in amount to that excreted when no adrenalin had been used. Further support of the independence of galactose utilization of factors which definitely modify glucose metabolism is shown in the results of Wierzuchowski.¹⁰ He found that the assimilation of galactose by dogs receiving a continuous injection of two grams of this sugar per kilo per hour over a 10 hour period was not affected by the type of previous food, by hunger, by adrenalin or by thyroxin.

Arcq¹¹ working with dogs and cats recorded that galactose, after either intravenous injection or oral administration, will augment hepatic glycogen but will fail to form muscle glycogen in spite of optimal conditions for its formation.

Laquer and Meyer¹² studying suspensions of muscle tissue found that dextrose and levulose were transformed almost quantitatively into lactic acid, while galactose was not converted at all, or in insignificant amounts only.

Griesbach¹³ in muscle perfusion experiments with galactose obtained no evidence of utilization. Very recently Roe and Cowgill¹⁴ failed to find any oxidation or conversion into glycogen of galactose in voluntary muscle tissue. They studied the galactose content of afferent and efferent blood in the leg in the dog following galactose administration.

Mann¹⁵ recovered from the urine more than 80 per cent of intravenously injected galactose in the dehepatized dog and more recently Bollman, Mann and Power¹⁶ have been unable to prevent the onset of hypoglycemic convulsions in the dehepatized animals with relatively large amounts of galactose. Roe, Gilman and Cowgill¹⁷ in 1934, from studies of the effect of the ingestion of galactose upon the respiratory quotient of the normal and depancreatized dog, reported that galactose per se is not oxidized in the dog, that its normal metabolism is conversion to an intermediate (glycogen) which may break down to glucose—a conclusion identical with that recorded by Shay, Schloss and Bell¹ in their studies on the human subject in 1931.

Despite the findings of Sheriff and Holmes¹⁸ that the presence of galactose prolongs the period during which the mammalian nerve consumes oxygen, indications are that this hexose does not play an important rôle in nerve cell activity. Galactose consumption by nervous tissue must be slight in view of the results obtained in depancreatized animals. Thus Kosterlitz and Wedler^{19,20} as well as Bollman and Mann²¹ have recovered in the urine amounts of galactose practically equivalent to those administered to depancreatized dogs. The excretion was recovered partly as glucose and partly as galactose.

Roe and Cowgill,¹⁴ by estimating the galactose contents of the blood samples removed simultaneously from the common carotid artery and from the internal jugular vein in dogs, after galactose administration, failed to obtain any evidence of the oxidation of galactose by nerve tissue.

In the clinical application of the galactose tolerance test certain facts, although previously published,²²⁻²³ must be reiterated. *This test can have no value if applied as a general liver function test. As an aid in the differential diagnosis of jaundice it is of incalculable value.* In the latter it has its greatest usefulness if applied early in the course of the jaundice.

The vital character of the carbohydrate function of the liver demands a large reserve in this organ. The remarkable regenerative capacity of the liver helps restore such a reserve. Impaired carbohydrate tolerance, therefore, becomes manifest only in the presence of acute diffuse liver cell damage, or in chronic damage, when the reserve has been spent and regeneration has failed. When diffuse damage has occurred and repair sets in, the carbohydrate function of the liver appears to be restored with great rapidity even when very little other change is discernible.

The galactose tolerance test, therefore, should be the first laboratory procedure employed in the study of jaundice. It is far more essential as an aid in determining therapy to know the galactose tolerance than it is to determine the number of milligrams of bile pigment in the blood or the icterus index. Aside from the fact that the tolerance should be determined early in the course of the jaundice, it should be repeated in two to three days if the results obtained are borderline. By a borderline reading we mean an output a little below 3 grams in the five hours of the test period.

In our work we have adopted the 3 gram level of urinary excretion of galactose as the upper limit of normal in the five hours after a 40 gram dose of the sugar. This figure we believe represents an adequate margin of safety. We have seldom under such conditions seen a urinary output of more than 2 grams in the normal individual. Owen⁶ has recently reported similar results. Readings between 2.5 and 3 grams, therefore, require a repetition of the test, in order to be able to interpret the results with certainty. Such readings usually occur in very mild forms of acute diffuse hepatitis, in which cases the readings may remain below 3 grams throughout the course of the disease. Then the short duration of the jaundice, the usually slight jaundice, as well as a rapidly diminishing galactose output to definitely normal levels on repeated testing, will indicate the mildness of the affection. Schiff and Senior²⁴ have recently reported such a case.

In other instances the carbohydrate function will be sufficiently disturbed to give a positive galactose test for only a short time and then will quickly return to normal as recovery rapidly sets in. Such cases indicate the importance of utilizing this test early in the course of jaundice. This point is illustrated by the following case.

J. F., aged 52, had been in excellent health until a week before admission when nausea appeared. About the same time jaundice was first noticed. There was no pain. A galactose tolerance test on the day of admission gave a reading of 3.46 grams, two days later a repetition of the test gave an output of only 2 grams, and three subsequent tests were all below 2 grams in spite of the fact that the blood bilirubin decreased very slowly.

Had the galactose tolerance test been delayed for two days, this case would have been classified under the failures for the test. The subsequent course and history indicated that we were dealing with a hepato-cellular jaundice which had had only a short period of disturbed carbohydrate function.

It is certainly no indictment of the test if it is found negative when applied first in the third or fourth week of a toxic hepatitis, at which time liver regeneration and repair in many instances will have been sufficient for the restoration of the vital carbohydrate function. Nor does it seriously impair the value of the test if it is found positive occasionally in an obstructive jaundice of several weeks' duration. By this time the reserve of the liver may have been overtaxed or the jaundice may have become associated with infection of the biliary tree which has had time to spread and

superimpose diffuse hepatic cell damage upon the initial obstruction. We believe that the few unfavorable reports on the galactose tolerance test in jaundice have been due to the failure to apply strictly the criteria which we have stressed in the interpretation of results and to a lack of consideration of the limiting factors imposed by the peculiarity of the liver itself, and not to a weakness of the test itself. All these difficulties can be avoided if the test is applied early in the course of the jaundice. The recent reports of Schiff and Senior, of Rosenberg²⁵ and of Tunen and Piersol²⁶ confirm this opinion.

A recent experience has indicated a possible explanation for some false positive results. As previously stated the metabolism of galactose is in all likelihood a conversion first to glycogen and then to blood glucose. Blanco,²⁷ Block and Weisz²⁸ and Harding and Grant³ have clearly demonstrated that a rise in blood glucose may follow the administration of galactose. The conversion of galactose to glucose in the diabetic too is indicated by the increased blood glucose found by Roe and Schwartzman⁵ after galactose ingestion. In normal rabbits, Roe and Cowgill¹⁴ found that the fall in blood galactose over a four hour period following this sugar sometimes occurred concomitantly with a gradual steady increase in blood glucose. It appears that the rise in blood glucose following the ingestion of 40 grams of galactose may be sufficient to result in an excretion of glucose in the urine in some cases of impaired kidney tubule absorption (so-called low kidney threshold). That this mechanism may be responsible for a false positive galactose tolerance test is indicated by the following instance. M. G., aged 42, presented a history and other data which appeared to indicate a complete common duct obstruction by a stone, yet the galactose output was 3.4 grams. In the absence of long standing jaundice or marked infection in the biliary tree, it was difficult to reconcile the galactose tolerance with the other findings. After fermentation of the urine, however, it was found that the galactose fraction was not over 2.1 grams, the additional 1.3 grams having been present in the form of glucose. A glucose tolerance test done subsequently on this patient yielded strongly positive urinary reducing reactions even though the peak of the blood sugar curve reached only 148 mg. of glucose per 100 c.c. of blood. We have been thus prompted to add the differential fermentation as a routine in all cases in which the urinary excretion after 40 grams of galactose is over three grams. We now carry out the fermentation test as follows:

A suspension of yeast in water is centrifuged, and the supernatant liquid is discarded. Fresh water is added to the yeast, the two are again mixed, centrifuged and again the supernatant liquid is discarded. At the third washing, the supernatant liquid is tested qualitatively for reducing substances with Benedict's or Fehling's solution. If none is present, the yeast is ready for use. Three or more washings are generally necessary for the preparation. Portions of this packed yeast are then transferred to 50 c.c. of the urine sample, and to 25 c.c. of an approximately 1 per cent solution of glucose. The two are then incubated for 30 minutes at 37° C. and the concentration of sugar again determined. The fermentation of the glucose solution

is included as a control on the activity of the yeast. The concentration of reducing substances remaining in the fermented urine is taken as the measure of the galactose excreted.

SUMMARY

1 The galactose tolerance test may be carried out with a fixed dose of galactose, since the utilization of galactose appears to be independent of age, weight or sex.

2 Because the utilization of galactose by tissues other than the liver is minimal or nil, and because of the absence of a kidney threshold for galactose, the urinary excretion after a standard dose of galactose may be taken as a measure of the carbohydrate function of the liver.

3 The determination of the blood sugar curve after galactose is of no value in measuring the utilization of the sugar, because its conversion to glycogen by the liver may alter the glucose content of the blood during the test. The determination of the blood galactose curve greatly detracts from the value of the test by complicating the technical procedure while adding nothing to the accuracy of the results.

4 *In the clinical application of the test the time at which the test is performed in relation to the time of appearance of the jaundice is of utmost importance.* The test has its greatest value and the results are most reliable when it is performed soon after the appearance of the jaundice. The longer the duration of the jaundice before the test is done the more frequently will the results be misleading.

5 Very mild cases of hepato-cellular jaundice may give a negative galactose test throughout the course of the disease. The other clinical and laboratory data will serve to identify this group.

6 The test has its greatest value in the painless jaundice group of middle and later life. If used early and judiciously in this group it will be of immense help in prognosis and will help prevent unnecessary surgery in the hepato-cellular jaundice of those age periods.

7 Because of the possibility of some glucose excretion after the dose of galactose in some disturbed endocrine states [thyroid, adrenal, pituitary, potential or mild unrecognized diabetes, or in cases of impaired renal tubular absorption (so-called low renal threshold)], we feel that differential fermentation of the urine with properly prepared yeast should be made part of the routine technic in all cases in which the excretion of reducing substances in the five hour urine exceeds 3 grams.

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NIGHT BLINDNESS AS A CRITERION OF VITAMIN A DEFICIENCY REVIEW OF THE LITERATURE WITH PRELIMINARY OBSERVATIONS OF THE DEGREE AND PREVALENCE OF VITAMIN A DEFICIENCY AMONG ADULTS IN BOTH HEALTH AND DISEASE^{*}

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IN contrast to the hundreds of papers concerning the experimental, chemical, and pathological aspects of vitamin A deficiency are the small number of clinical studies. Such clinical investigations as are available deal, for the most part, with infants and children, and until recently, the manifestations of deficiency in adults have been overlooked or ignored^{1, 2, 3}

Probably few physicians in this country are aware that there are now available several methods of quantitatively estimating the degree of vitamin A deficiency in humans, and further that some of these methods are simple enough for routine clinical use. Investigations in Europe and this country have shown that our conception of the prevalence of avitaminosis must be revised. In this country, Jeans and Zentmire⁴ and Sandler⁵ have investigated the prevalence of vitamin A deficiency in children. However, there have been no studies on adults using this technic, except by Park,^{6, 7} whose work has appeared since the inception of this investigation.

It is the purpose of this paper to report some observations concerning the degree and prevalence of vitamin A deficiency among a group of supposedly normal adults and also to give some preliminary results obtained by testing persons afflicted with various types of diseases. The important literature dealing with vitamin A deficiency will be briefly reviewed, since much of it is widely scattered and a proper orientation is necessary to understand the significance of the newer developments in this field.

PHYSIOLOGY AND BIOCHEMISTRY OF VITAMIN A

To truly appreciate the clinical manifestations of vitamin A deficiency, it is necessary to know where and in what form the vitamin is found, what happens to it after ingestion, where it is stored in the body and the rôle it plays in conditioning functional activities of humans.

The vitamin A content of our diet comes from two distinct sources, namely alpha, beta, and gamma carotene and cryptoxanthin (grouped under the designation carotene or carotenoid substances for convenience) from the plant kingdom, and true vitamin A from certain animal tissues⁸

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Animals and humans are unable to synthesize either carotene or vitamin A in their bodies and must depend on exogenous sources for their supply. The carotenoid substances are synthesized by plants, and from them the animals of both land and water derive their supplies either directly, or indirectly by preying on other animals.⁸

A recent editorial in the *Journal of the American Medical Association*¹⁰ summarizes the differences between carotene and vitamin A as follows: "They are not identical substances: carotene is yellow, whereas vitamin A has little color; vitamin A exhibits an absorption of light of wave length 328 millimicrons, carotene does not, both give a blue color with antimony trichloride but that with vitamin A shows an absorption band of 619 millimicrons, whereas that with carotene absorbs light of wave length 590 millimicrons. Carotene is a crystallizable hydrocarbon with a cyclic structure, related to the terpenes, and the recent evidences indicate that vitamin A is probably a primary alcohol derivative of one half the carotene molecule."

Being fat soluble substances, both carotene and vitamin A are absorbed by the lacteals of the intestine, become intimately associated with the chyle and enter the general circulation through the thoracic duct.¹¹ No change in either substance takes place during the absorbing process. Vitamin A is directly stored in the liver until used by the body. Carotene is changed to vitamin A in the liver by an enzyme called carotenase, one molecule of carotene giving rise to two molecules of vitamin A.¹² The liver also plays an important part in the regulation of the concentration of the vitamin throughout the remainder of the body.⁹ Examination of livers of healthy humans killed by accident, shows that the vitamin A content tends to remain constant within certain limits.¹³ However, when the diet was poor the amount of this vitamin stored in the liver was found to be less than normal.

Rowntree¹⁴ was able to show that even after the ingestion of an excess of the vitamin only 2 to 12 per cent was lost in the feces. Green¹⁵ believes that the urinary excretion does not account for any significant loss and that if taken in excess, the unstored portion of the vitamin is destroyed in the liver or oxidized in the blood stream.

When this vitamin is entirely absent from the diet, experimental work suggests that it takes several weeks or longer to deplete the liver store and cause vitamin A deficiency to become manifest clinically.⁹

Fever,⁸ rapid growth,¹⁰ general infection,¹⁷ elevated basal metabolic rate,¹⁸ and pregnancy¹⁹ all increase the metabolic need for vitamin A. Lack of bile²⁰ or pancreatic secretion,²¹ changes in the gastrointestinal mucosa,⁷ and disturbances of motility of the gastrointestinal tract¹⁷ all prevent or hinder the proper absorption of this vitamin. Liver disease¹⁷ prevents the proper storage of vitamin A as well as the conversion of carotene to vitamin A. Any of these mechanisms can lead to vitamin A deficiency even though the amount of the vitamin in the diet is theoretically adequate.

Both carotene and vitamin A are effective when given parenterally⁹

The functions of vitamin A have not been entirely settled. Its growth promoting and anti xerophthalmic functions are well established⁹. Mendel⁹ is not sure whether it is a 'necessary integral part of structures like the epithelial cells or whether it acts as a catalyst or as a "regulator" of certain cellular functions. The anti-infective nature of this vitamin has been the subject of much controversy. The most reasonable stand is taken by Mendel⁹ who believes "that its influence is felt indirectly in that the vitamin helps to preserve the physiologic integrity of various epithelial structures and thus to maintain the 'first line of defense' against the invasion of bacteria."

It seems to matter little whether the vitamin is present as pure vitamin A or carotene in our food. Cow's milk, human milk, eggs, animal livers, cod-liver oil and cheese all contain adequate amounts of vitamin A. Butter contains both vitamin A and carotene. Spinach, watercress, carrots, green peas, lettuce, oranges and tomatoes are among the better sources of carotene. Storage, bleaching, oxidation and other processes may reduce the vitamin activity of any food⁵.

PATHOLOGY OF VITAMIN A DEFICIENCY

Eusterman and Wilbur²² in their review wisely suggest that a broad view of the pathology of vitamin A deficiency be taken and that attention be not, as in the past, concentrated chiefly on changes in the ocular organs. Wolbach and Howe,^{23, 24} Goldblatt and Benischek²⁵ and many others have shown by experimental studies that specific changes in the tissues in vitamin A deficiency affect primarily the epithelial tissues, and consist of substitution of keratinized stratified squamous epithelium for normal columnar epithelium. Such changes were found in the eyes, para ocular glands, genito-urinary tract, alimentary tract and respiratory tract. Emaciation and atrophy of glandular organs were occasionally found. There is at present question whether or not the central nervous system is involved²⁶.

Pathologic studies of avitaminosis A in human beings, although few in number, have been considered to show lesions identical with those found in experimental rats^{21, 27, 28}. This aspect of the subject has been reviewed recently by Blackfan and Wolbach²¹ and Sweet and K'Ang². To the basic animal work have recently been added the histological studies of the skin lesions in humans²⁹.

Since intact, healthy epithelial membranes, which constitute the first line of defense against bacterial invasion, are destroyed by vitamin A deficiency, secondary infection commonly complicates the more advanced cases and is the cause of most of the deaths².

Blackfan and Wolbach,²¹ in studying humans, were able to show at postmortem examination that often various tissues showed microscopic evidence of vitamin A deficiency even though grossly the organs appeared

normal and during life the patient presented no gross clinical evidence of vitamin deficiency. Since they studied small children or infants, it was impossible to state whether or not hemeralopia existed during life.

These observations are important in that they suggest that mild degrees of vitamin A deficiency (such as can be detected by the photometer) may be associated with microscopic changes in various epithelial tissues throughout the body.

CLINICAL PICTURE OF VITAMIN A DEFICIENCY

It is generally accepted now that in adults and older children, essential hemeralopia (night blindness) is almost always the earliest manifestation of vitamin A deficiency^{1, 2}. In infants and small children this symptom is of course easily overlooked. In contrast to infants, where the disease progresses rapidly, hemeralopia may for many years be the only manifestation in adults^{1, 10}. It is also accepted that even severe degrees of hemeralopia can exist without ophthalmoscopically demonstrable changes in the eye being present^{1, 31}.

As the degree of avitaminosis A progresses gross anatomical changes occur in the eye. Pillat¹² considers dryness of the conjunctiva (xerosis) to be the usual second stage of this disease. Both bulbar and palpebral conjunctivae may be dry and lustreless and contain spots (Bitot's spots) which have the appearance of foam or frost on a window pane. In size the spots may vary from tiny specks to areas large enough to cover the whole scleral area beyond the cornea. They are firmly attached to the conjunctiva and wrinkle peculiarly as the eye-ball is moved. There is lessened secretion of tears due to the inactivity of the para-ocular glands. The process at this stage is reversible under proper therapy. Excellent illustrations of Bitot's spots can be found in the papers by Spence³⁰ and Pillat³³.

Keratomalacia is the last stage of the eye manifestations in adults as well as in infants³². This condition results from corneal softening which allows secondary infection to take place, and often leads to destruction of the eye and blindness. Pigmentation of the conjunctivae, giving the appearance of argyrosis, has been noticed, particularly in the dark skinned races^{33, 34}. Meibomitis, blepharitis, hordeolum and edema and puffiness of the eyelids are common³³. Insensibility of the cornea, almost to complete anesthesia, is frequent³⁵.

By the time the second or xerotic stage in the eye is reached, other manifestations of avitaminosis A are noticed elsewhere in the body. This is, of course, in keeping with the pathological demonstration of widespread metaplasia of epithelial tissues.

Bronchopneumonia, bronchitis, bronchiectasis, infections of the nose and accessory sinuses or hoarseness are commonly seen when xerosis or keratomalacia is present, and indeed one of these complications (especially bronchopneumonia) is a common cause of death in vitamin A deficiency.

Probably next to the eyes, the skin undergoes the most marked and extensive change of all.² Dryness is the most frequent, but least characteristic change. Itching may occur. The most specific cutaneous lesion was described by Frazier and Hu,²⁹ and since repeatedly confirmed^{36, 37} The lesions vary from a slight roughening of the skin to papular cornified lesions surrounding the hair follicles, and are usually more marked over the extensor surfaces of the extremities and over the shoulders. The dry skin results from the deficient function of the sebaceous and sweat glands. Numerous comedones on the face are frequent. Hair may become dry, coarse and brittle, and fall out. In infants and small children the skin manifestations are limited to dryness, scaliness and shriveling, and only rarely show the keratinized plugs in the hair follicles. Frazier²⁹ and Mackay³⁸ believe that skin lesions may exist before xerosis is present and are a valuable sign of avitaminosis A when the presence of hemeralopia cannot be ascertained (as in children or when a photometer is not available for testing adults).

Loss of weight, weakness, genito-urinary infections,² diarrhea² and mild anemia³⁹ are less frequent and less characteristic manifestations. The relationship in humans between the lack of vitamin A and the formation of kidney stones is still controversial,⁴⁰ as is that between avitaminosis A and the common cold.⁴¹ Laboratory studies yield variable results.² A temperature of 101° to 104° F (aside from that due to infection) may be present in the second and third stages in adults, and disappears in a few days under therapy.³³ A detailed discussion of the clinical picture can be found in the papers by Eusterman and Wilbur,²² Blackfan and Wolbach,²¹ Sweet² and Mackay.³⁸

It should be appreciated that manifestations of avitaminosis A (other than hemeralopia), while rare in this country, continue to be the subject of periodic reports.^{42, 43, 44, 45} If hemeralopia were searched for, probably most cases of vitamin A deficiency could be diagnosed before any gross changes had taken place.

NIGHT BLINDNESS

Night blindness, often called hemeralopia, *dysaptatio visualis*,⁴⁶ *hesperanopia* (French),⁸² *nyctanopia*,⁸² *nutritional dyskotopia*^{47, 48} or erroneously *nyctalopia*, is the difficulty, and occasionally, inability to adapt the faculty of vision to very faint illumination.

There has been in the past considerable confusion as to the nomenclature of day blindness and night blindness. The terms hemeralopia (literally meaning day sight) and nyctalopia (meaning night sight) have been used interchangeably so often that the best usage of these terms is difficult to decide. Most modern authors and the "Quarterly Cumulative Index Medicus" list night blindness as hemeralopia. Edmund⁴⁶ suggests that the term nyctalopia, be used to designate the condition of being more easily dazzled by light than normally and hemeralopia be used to indicate a reduction of visual function in reduced illumination.

Hemeralopia (night blindness) may develop in many conditions causing changes either in the light-refractive apparatus of the eye or in the light-perceptive apparatus¹. The first group is made up by affections of the cornea, anterior chamber, lens or vitreous humour. Conditions which can cause changes in the light-perceptive apparatus and cause hemeralopia include retinitis, choroiditis, retinitis pigmentosa, detachment of the retina, optic atrophy, optic neuritis, sympathetic ophthalmia, glaucoma, excessive myopia, poisoning (quinine, carbon disulphid, various war gases, etc.) and Oguthis' disease.

Grouped under changes in the light-perceptive apparatus is essential or idiopathic hemeralopia due to vitamin A deficiency. *In this type of hemeralopia, however, there are no ophthalmoscopically demonstrable changes in the eye.*

There is now abundant evidence available to show that in older children and adults, essential hemeralopia is usually the earliest and the most constant manifestation of avitaminosis A,^{1,2} and that it may exist for years without any other sign of the deficiency appearing.³ Only severe degrees of night blindness annoy the patient sufficiently to cause him to seek medical attention.⁴ In this country, such cases are fairly uncommon as compared to the milder to moderate forms of hemeralopia which can be detected only by the methods to be described.⁵ It is only beginning to be appreciated that a mild to moderate degree of night blindness may be present and interfere with the efficacy of dark adaptation and visual acuity in dim illumination without the person being aware of its existence.¹

According to the duplicity theory of vision, the eye has two distinct mechanisms for sight. Photopic vision occurs only with light of moderate or high intensity and is essentially a function of the cones. With this type of vision objects are seen in their true color. Vision under faint illumination (scotopic vision) is mostly peripheral and primarily a function of the rods. If a spectrum of low intensity is viewed with the dark adapted eye it appears as a gray band differing in brightness in different parts. In other words, with dim vision objects are only seen as different intensities of gray. Rod function (scotopic vision) depends upon the metabolism of the phototropic substance known as visual purple (rhodospin) of the retinal rod cells. Since, as it will be shown later, visual purple is formed from vitamin A, it follows that scotopic vision is intimately associated with the available supply of this vitamin. Practically all tests commonly performed on eyes (i.e. visual acuity, depth perception, accommodation, test for color blindness and ocular muscle balance) are conducted in good illumination and therefore depend on cone function. Since cone function does not depend upon a supply of visual purple or vitamin A, we can appreciate how a person may rate 100 per cent in all these tests and still be so night blind as to scarcely be able to get about in dim illumination. Also since none of these tests will detect night blindness, we can appreciate why mild degrees of this condition were readily overlooked in the past. It explains in addition why the special

tests to be discussed later must be utilized in testing for night blindness. It is well known that animals or birds lacking in cones can see only at night (rod vision) and those lacking in rods can see only in bright daylight (cone vision). In the human eye the rods are more numerous at the periphery and sparse about the fovea. This explains why scotopic vision is mostly peripheral. The periphery of the retina is sixty times as sensitive to light as the central parts. The cones on the other hand are more numerous about the fovea and diminish as the periphery is reached. Therefore photopic vision is more acute in the central portion of the eye.⁴⁹

Visual purple (rhodospin) is very sensitive and becomes bleached and inactive when exposed to light (sunlight or artificial light) and rapidly regenerated if an adequate supply of vitamin A is present in the body. The chemical change which takes place during this bleaching of visual purple gives rise in the rods to impulses which are carried by the optic nerve to the brain and result in the registration of sight in terms of light and darkness.

Vitamin A has been shown to be the precursor of visual purple^{50, 51} and the vitamin is present in large amounts in the retina^{52, 53}. A deficient intake of this vitamin causes the body stores to be low and this in turn leads to slow and poor regeneration of visual purple. An inadequate supply of regenerated visual purple causes the retinal rod cells to be less sensitive to light, and this in turn causes poor vision under faint illumination (hemeralopia).

Wald^{52, 54, 55} has done much to clarify the relationship between visual purple and vitamin A, and was able on frogs to work out the following cycle of vitamin A in the eye.

Vitamin A, by means of a thermal reaction, is changed to visual purple which is a conjugated protein. Exposure of visual purple to light causes the purple color to disappear and allows the yellow or orange colors due to retinene (visual yellow) to appear. Visual purple is synthesized in the retina, either by reversion from visual yellow (retinene) or by regeneration from a fresh supply of vitamin A. During this cycle, a certain amount of these substances is lost, necessitating the arrival of a constant supply of vitamin A in the blood stream.

Night blindness (hemeralopia), as a symptom, has been known since the time of the ancient Egyptians and Hippocrates.² Even the beneficial results of liver therapy were described by Paul of Aeginta.⁵⁶ Hemeralopia of a marked degree has been described repeatedly in the literature as occurring in prisoners, inmates of asylums, soldiers in barracks, in religious groups during fasts, in crews of vessels on long voyages, in starving people during famines or long sieges.¹ What was described by the old sailors as moon blindness was undoubtedly night blindness⁵⁶ and the older literature suggests it was as common as scurvy. During the World War, hemeralopia was very common in the soldiers of the Central European Armies, often rendering large groups unfit for night duty.^{1, 57, 58}

It has been shown, in experimental animals⁵¹ as well as in humans,³¹ that hemeralopia becomes much more manifest in vitamin A deficiency after the eye has been exposed to light. A person who remained in a dimly lighted room all day would need but little visual purple to carry on his visual needs, as compared to a person who remained in the sunlight all day. Aykroyd³¹ reports that on the Labrador coast, night blindness was common and severe in those fishermen who were outdoors all day in open boats and either much rarer or milder in those persons who remained indoors and worked at other trades, in spite of the fact that all persons ate the same type of food. Evidence was also presented which showed that no amount of exposure to sunlight could cause hemeralopia to appear if the diet contained a normal supply of vitamin A. Aykroyd³¹ found further that it was the custom among some persons in Newfoundland and Labrador, where severe vitamin A deficiency was common, to wear a bandage over one eye while the other eye was left uncovered in order to see to carry on the day's activities. After dark they would remove the bandage. The eye which had been exposed to the sunlight would be night blind, but the other eye, which had been covered, would not be so severely affected and served them for sight until the next morning, when the procedure was again repeated. Wearing dark glasses during the day time also helped persons with night blindness to have better visual acuity after dark.

As will be shown later, mild to moderate (and occasionally severe) degrees of hemeralopia due to vitamin A deficiency are fairly common among many supposedly healthy adults, both in this country and in Europe. An important conclusion to these studies is that this large group of individuals, without in most cases being aware of it, have vision which while normal in daytime, is inefficient in dim illumination. The degree of this inefficiency would vary, of course, directly with the degree of vitamin A deficiency which was present.

Certain important practical problems dealing with essential hemeralopia in persons who drive automobiles at night, aviators and workers in certain trades, have been discussed in detail elsewhere by Jeghers⁵⁹. Chief among these has been the effect of minor and mild degrees of hemeralopia upon the skill of a person who drives an automobile at night.

Several persons were found who had night blindness severe enough to cause them to complain of difficulty in driving at night for fear of accidents and of being easily dazzled by the lights of oncoming automobiles. Many mild hemeralopics were found who drove automobiles and were unaware of this lowered visual acuity for dim illumination. Where tried, therapy caused complete relief of these symptoms and improvement in the ability to drive at night. In night driving we have what amounts to a perfect experiment to bring out hemeralopic manifestations if vitamin A deficiency exists. The glare from the lights of each oncoming car depletes a fraction of the visual purple. If the person has avitaminosis A, regeneration is slower than normal and not complete at the time. Several hours of night driving could

easily decrease the skill of a vitamin A deficient person to the point where his chance of having an accident would be greatly increased. Being an individual affair, automobile driving at night does not enable one to compare directly his skill with that of a person with normal dark adaptation. Hence, many persons probably accept minor degrees of difficulty in night driving as the usual experience of all drivers.

Park,⁶ Vignalon,⁶⁰ Rollet,⁶¹ Wilbur and Eusterman,¹⁷ and Tilderquist⁶² have all reported instances of hemeralopics who had accidents or marked difficulty in driving automobiles at night, and where vitamin A therapy was tried, all obtained relief. Mason's⁶³ survey shows that in this country a test for essential hemeralopia is not at present required of any candidate for a driver's license.

As defined by Edmund,⁴⁸ nyctalopia signifies the condition of being more easily dazzled by light than normally. In other words, a person with nyctalopia complains of being dazzled by an illumination which has no dazzling effect upon normal persons. While nyctalopia can be due to various eye diseases, Edmund has shown that it is present in many persons with hemeralopia and vitamin A deficiency, and that it will disappear after vitamin therapy. What is commonly known among autoists as "glare blindness" due to exposure to bright lights while driving at night, may be a manifestation of vitamin A deficiency in an as yet undetermined percentage of the cases. An extensive survey of the incidence of hemeralopia and "glare blindness" among automobile drivers is at present under way and will be reported upon later.

It has been amply demonstrated that normal visual acuity, as usually tested, is no guarantee against the presence of night blindness. Frandsen¹ had many hemeralopics with 20/20 day vision who had very poor vision in dim illumination. Likewise, it has been shown that mild to moderate degrees of hemeralopia are accepted as the normal situation, unless skill in performing an act in diminished illumination is compared to the simultaneous performance of a similar act by a person with normal dark adaptation.⁵⁹ For instance, a person with mild vitamin A deficiency will have more difficulty in going from bright daylight into a darkened cinema and find his way to a seat than will a person with a normal supply of vitamin A.

METHODS OF DETECTING VITAMIN A DEFICIENCY

In the past, vitamin A deficiency was not recognized until marked hemeralopia, xerophthalmia or keratomalacia developed. It should again be emphasized that these manifestations represent severe and well advanced degrees of avitaminosis A, and are rare compared to the milder, and often clinically undetectable, degrees of deficiency.

For many years, foreign investigators have been using various types of photometers to measure quantitatively minor to moderate degrees of night blindness.^{1, 57} It was also discovered empirically that hemeralopia not due

to intra-ocular disease would respond to food rich in vitamin A, with a subsidence of the symptoms and a return of the photometer reading to normal^{57, 58} The experimental demonstration by Fridericia and Holm⁵⁰ and Tansley⁵¹ that vitamin A was necessary for regeneration of visual purple, the studies by Holm⁶⁴ by means of a jumping test conducted in a dimly lighted room, that hemeralopia was the first manifestation of vitamin A deficiency in rats, along with the numerous clinical studies showing the relationship between marked hemeralopia, *xerosis conjunctivae* and keralomalacia, and avitaminosis A^{65, 66, 67} led to the logical conclusion that such photometer tests could be used to detect sub-clinical degrees of vitamin A deficiency

In a recent monograph on the subject, Frandsen¹ summarizes the objective data concerning essential hemeralopia as follows "These patients show an *increased minimum light visible* In *reduced illumination* the acuity of vision is lowered, the field of vision for blue in higher degrees of hemeralopia becomes smaller than the field for red Dark scotoma appears at higher clarity than in the case of normal light sense, the adaptation time is prolonged, the power of distinction is lowered—all signs which signify that the range of adaptation is reduced"

One of the following methods listed by Edmund⁶⁸ and Frandsen¹ can be used

Method One

Minimum light visible determination (faintest light which the eye can detect) sometimes together with plotting of adaptation curves

Method Two

Visual field examination at reduced illumination

Method Three

Visual acuity determinations at reduced illumination

Method Four

Examination of distinction power

I The first method involves the use of a photometer Although various types of photometers can be used,^{1, 68} the Birch-Hirschfeld photometer, introduced by Birch-Hirschfeld in 1916,⁵⁷ has been used for clinical studies in Europe,¹ China⁶⁹ and in the United States^{4, 5, 6} with good results In 1934, Jeans and Zentmire introduced in this country the Birch-Hirschfeld photometer as a means of measuring minor degrees of vitamin A deficiency The mechanism and use of this instrument are described later

An American firm has recently perfected a new photometer called the "Bio-Photometer" * (see figure 1) Since it was designed primarily for routine clinical use it will undoubtedly displace many of the more cumbersome photometers now on the market It operates on the principle of measuring the minimum light visible and has the advantages of greater

* The Bio-Photometer is manufactured by the Frober-Faybor Company, Cleveland, Ohio

portability, compactness, and of measuring the minimal light intensity which the eye can see directly in milli-foot candles. This photometer can measure differences of one-millionth of a foot candle of light. This obviates the necessity of standardization of the instrument by the operator and allows readings obtained by one instrument to be compared directly to another. In addition, a standard source of bleach light is provided within the instrument.

Jeans et al.⁸³ have recently given their experience with this photometer and explain the technic of its use. Since readings can be made in a few



FIG 1 The bio-photometer. This instrument is compact, made in portable models, contains a standard light within the instrument for bleaching visual purple and measures the minimal light visible directly in milli-foot candles. (Photograph courtesy of the Frober-Faybor Company, Cleveland, Ohio)

seconds, the adaptation curve in the dark can be plotted instead of merely depending on a reading at the beginning and end of the dark adaptation period, such as in the Birch-Hirschfeld technic. Jeans et al.⁸³ were able to show that the "Bio-Photometer" is more sensitive than the Birch-Hirschfeld and will pick out border line cases of deficiency missed by other methods.

II Visual field determinations serve as the second method of detecting essential hemeralopia and are according to Edmund⁶⁸ accurate and satisfactory for experimental studies but too complicated for routine use. *It is important that the test be done under reduced illumination and standard-*

ized on subjects with no intraocular disease and ingesting an adequate supply of vitamin A, if one wishes to detect minor degrees of hemeralopia

Kiang,⁷⁰ studying subjects in China by the perimeter method, found concentric contraction of the visual fields with the blue field smaller than the red. The contraction of the color field was proportional to the severity of the deficiency. Following vitamin A therapy, the visual fields returned to normal size while the blue field became larger than the red.

III The third method, examination of visual acuity at lower illumination, has been employed by a great many authors and gives a good expres-

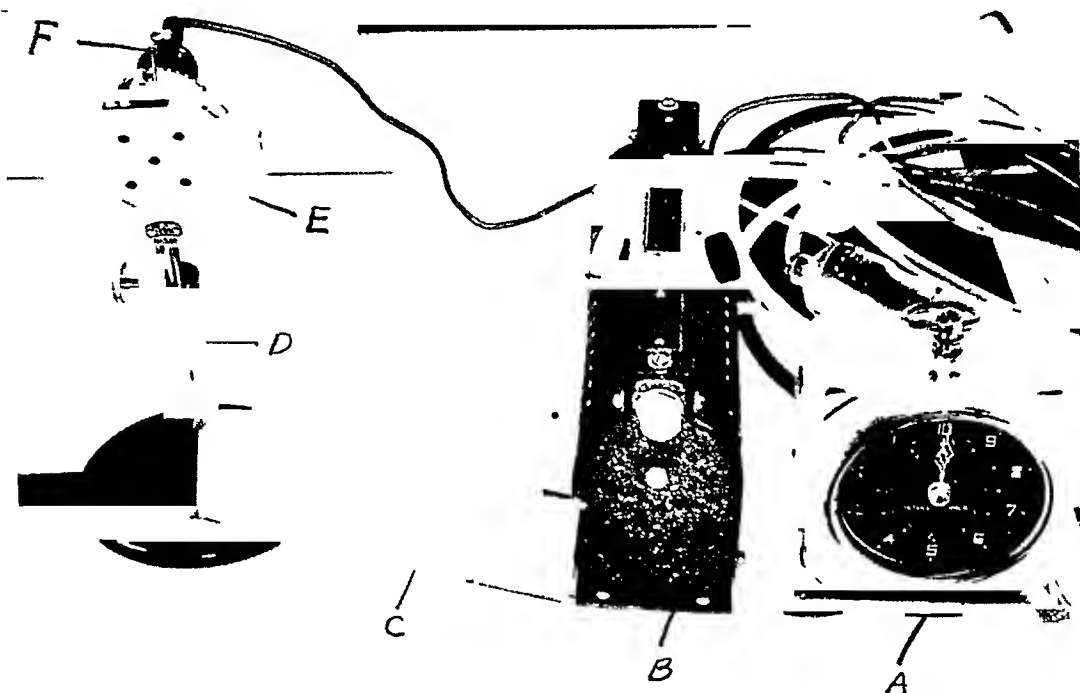


FIG 2 Birch-Hirschfeld photometer used in experiments (a) The time clock (b) The rheostat for reducing current for photometer light (c) The Goldberg wedge (d) The Birch-Hirschfeld photometer (e) The 5 point disc (f) Handle which controls the aperture of the diaphragm. Directly behind (f) is the housing of the photometer light. The Goldberg wedge (c) slides into grooves before the 5 point disc (e).

sion of light sense of the eye, but is not a suitable method for routine clinical examination.¹

IV The fourth method, examination for distinction power, has been used extensively by Edmund,³ Frandsen¹ and others in Denmark. This test requires the use of a set of eight Tscherning photometric glasses combined with Edmund's test charts. (See figure 3.) The photometric glasses are neutral-gray glasses, which absorb the passing light after a logarithmic scale, so that glass number 1 transmits $1/10$ of the light, glass number 2— $1/10^2$, etc., to glass number 8 which transmits $1/10^8$ of the light. The test chart of Edmund consists of gray letters E of varying intensity on a white back-

ground The distinction power is 0.00 when only the darkest letter can be seen, 0.25 if the next darkest E can be seen, etc., increasing by steps of 0.25 until a distinction power of 2.00 is needed to see the faintest letter

The test is conducted by illuminating the test charts with a standard light (details can be found in the monograph by Edmund³) The darkest glasses (number 8) are placed before the subject's eyes After complete



FIG 3 Tacked on the upright board are the nine test charts devised by Edmunds. Each consists of the letter E, gray in color, on a pure white background. The darkest E measures a distinction power of 0.00, the next E measures a distinction power of 0.25, rising in steps of 0.25 until a distinction power of 2.00 is reached for the faintest E. The subject (facing the camera for illustrative purposes) is wearing a special pair of light-proof goggles into which the Tscherning photometric glasses fit. Two of the glasses are lying free on the table, along with an extra pair of goggles. The box on the table contains the complete graded set of Tscherning photometric glasses. The light which illuminates the letters is not shown. The fainter letters E are not visible on this photograph. During the test the subject reads the test charts at a distance of 25 to 50 centimeters.

adaptation in the dark, the subject is shown the illuminated charts. The faintest E which can be seen is the distinction power of the eye for illumination of glass number 8. The subject then closes his eyes and glasses number 7 are substituted for number 8 and the distinction power determined for glass number 7. This is repeated in turn for glasses number 6, 5, 4, 3, 2 and 1. The final reading is made without any glasses before the eyes. These values can be plotted on a graph (see figure 4). A typical normal

and also a curve from a vitamin A deficient person is shown. With vitamin therapy the deficient curve gradually approaches the normal curve. This method has the advantages of being independent of refractive errors, requires no training or intelligence on the part of the subject and the end point can be made objective by turning the E in various directions. The charts are read at a distance of 25 to 50 centimeters and a visual acuity of only 6/36 is needed to see them. This method of testing would be ideal

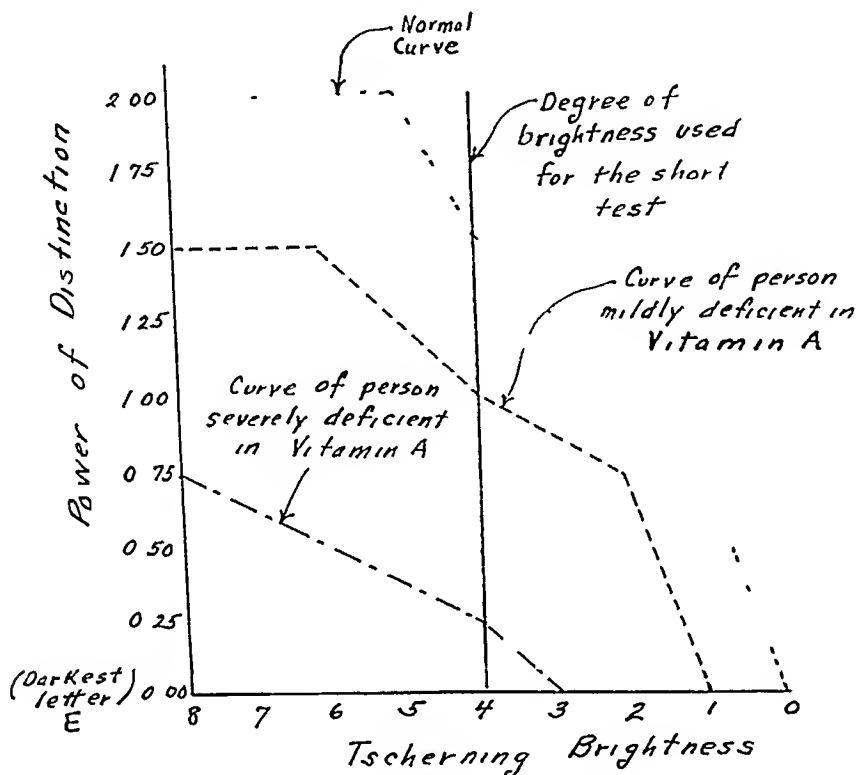


FIG 4 Typical curves obtained when the power of distinction is plotted for different degrees of dim illumination. With proper vitamin A therapy the deficient curves gradually improve to coincide with the normal curve. The ability to see the darkest letter E is considered a power of distinction of 0.00. A distinction power of 2.00 is needed to see the faintest E. (Modified after Edmund)

for aviators, because using this principle a test for spatial discrimination in dim illumination could be devised.

Edmund³ has shown that the test can also be shortened by using only one determination, usually with the Tscherning photometric glass number 4. This test takes but a few minutes.

The writer is at present conducting an extensive study of vitamin A deficiency comparing Edmund's method and the Bio-Photometer. These results will be published later.

Prior to use of these tests for hemeralopia as a measure of vitamin A deficiency, other laboratory procedures were used for detecting mild degrees

of deficiency of this vitamin. Many workers ^{2, 21, 30} have suggested examining the urine, tracheal secretions, or scrapings from the nasal mucosa or conjunctivae. In any of these, the demonstration of cornified epithelial cells is considered presumptive evidence of avitaminosis A. While useful in the hands of experts, these methods are crude, positive in only the more advanced cases and non quantitative as compared to the visual procedures described.

Carr and Price ⁸⁴ found that antimony trichloride produced a blue color with vitamin A. This test can be used to detect the amount of vitamin A present in the blood stream. Attempts are being made to develop this into a clinical test of vitamin A deficiency ⁸⁵. Further studies may prove this to be a valuable adjunct to study and diagnosis of vitamin A deficiency. It has been shown that the amount of vitamin A in the blood stream varies with the diet, age and infection. What is needed is a series of studies correlating the blood vitamin A and carotene with measurements of night blindness and response of each to proper therapy.

Unfortunately tests for vitamin A deficiency which depend upon some objective manifestation of hemeralopia cannot be satisfactorily used on children under the age of five, due to the lack of intelligent cooperation. This leaves an important group with no test for sub-clinical degrees of vitamin A deficiency.

Quite recently, there appeared the preliminary report of a method which promises to be applicable to this at present undiagnosable group. Fride-richsen and Edmund ⁷¹ were able to work out a method of detecting minor degrees of vitamin A deficiency which is quantitative and could be used to test children even during the first two years of life.

This method depends upon determining the faintest light irritant (minimum reflexible) that is able to provoke an oculomotoric reflex. The magnitude of the required irritant was proved to be fairly constant in normal infants and to depend on the power of adaptation. In infants who are not adapted to darkness a stronger light irritant is required to provoke ocular reflexes than in children adapted to darkness. Measuring the magnitude of the light irritant required in infants who have had the opportunity of adapting themselves to darkness makes it possible to obtain a quantitative idea of the presence of hemeralopia and indirectly the degree of vitamin A deficiency. Follow up studies with this technic ⁸⁸ have shown that vitamin A deficiency is common in infants. Rapid return to a normal minimum reflexible followed vitamin A therapy in those who had low readings.

TECHNIC

The Birch-Hirschfeld photometer * was used in this study (figure 2). The technic of its use and working mechanism are described in detail in the papers by Birch-Hirschfeld ⁵⁷ and Jeans and Zentmire ⁴.

* The Birch-Hirschfeld Photometer was of Zeiss manufacture.

The instrument consists essentially of a metal tube with a light of constant illumination at one end and an iris diaphragm at the other end. This diaphragm allows the aperture to vary from two to 20 millimeters in 10 separate steps. A metal disc containing five holes punched out in the five point quincunx of the throw dice is placed before the diaphragm. In front of the disc slides a Goldberg wedge. This wedge is essentially a glass slide of 13 different opacities, ranging from complete transmission of light at the left end and zero transmission of light at the right end. Various combinations of the 10 diaphragmatic apertures and the 13 different degrees of opacities on the wedge give over 100 finely graduated steps of light intensity.

A light proof dark closet was prepared on each of two wards, with one wall painted white to facilitate bright illumination. The subject was seated facing the white wall in a position similar to that used by Jeans and Zentmire⁴ with the eyes 60 centimeters from the photometer scale and 100 centimeters from the wall.

After exposure of the eyes for five minutes to the indirect light from a 200 watt electric bulb which shines on the white wall (to use up visual purple), the room was made completely dark and an initial reading was taken of the faintest light which the subject was able to see (minimum light visible).

The two holes on the left of the disc, the center hole and the two holes on the right side of the disc were each covered by a different opacity on the Goldberg wedge. In closing the diaphragm the holes on the right disappeared first, then the center hole and finally the left two holes. The point at which the right hand holes disappeared and the center and left hand holes were just visible was recorded as the end point. It is best to begin with a wedge opacity reading of three. If the light from the two millimeter aperture of the diaphragm can be seen as described above, then the wedge opacity is set at four, the diaphragm opened to 20 millimeters and reduced step by step. If, however, on the first wedge opacity tried, the light from the 20 millimeter aperture is not seen, a less opaque wedge setting is used and the process is repeated until the proper arrangement of the lights is finally read.

The eyes were then allowed to accommodate in total darkness for 10 minutes and the reading on the photometer repeated. As the visual purple regenerates fainter and fainter light intensities can be detected. The regeneration time period must be kept constant and timed with an alarm which rings a bell. It is important that during this period no lights of any kind be used in the room.

For this reason it is necessary to memorize the clicks as the wedge and diaphragm position are shifted so that the final reading can be obtained in complete darkness. This is readily accomplished after a short period of practice.

Each reading consists of the wedge position—varying from zero (no opacity) to 13 (complete opacity) and the iris diaphragm aperture varying from two millimeters to 20 millimeters in steps of two millimeters.

The entire procedure takes less than 20 minutes. The photometer, before being used, must be standardized on a group of healthy adults who have taken vitamin A concentrate for several weeks or have had an adequate diet for several months, as well as being free of any intra-ocular disease. In performing the test, a few subjects were troubled with "after images" and were not sure of the end point. This was particularly apt to happen if a long time was taken to reach the proper wedge opacity for the final aperture reading. Skill in handling the photometer and alert cooperation on the part of the subject will minimize this difficulty. Also covering the photometer scale for 10 to 20 seconds to rest the subject's eyes and repeating the reading usually enabled a satisfactory end point to be reached. Those persons who wore glasses were asked to do so during the test. However, this

is not absolutely necessary since Frandsen¹ was able to show that minor refractive errors played no part in causing hemeralopia

It is important to be sure that no intra-ocular condition is present which can cause night blindness, before assigning the lowered photometer readings to vitamin A deficiency

Edmund³ and Frandsen¹ have shown that familiarity with this general method (by repeated trials) did not change the reading of distinction power obtained. In the present series, repeated tests at monthly intervals on several subjects and often by different operators gave essentially the same reading

RESULTS AND DISCUSSION

A total of 274 satisfactory photometer tests were performed. The results are summarized in table 1. The subjects were divided into three groups as follows

Group I Consisted of 22 physicians who ate in the doctors' dining room at the Boston City Hospital

Group II Consisted of 149 subjects comprising WPA employees, medical students, technicians and graduate nurses

Group III Consisted of 103 ambulatory patients. Tests in this group were usually made shortly before discharge

TABLE I
Summary of 274 Photometer Tests for Vitamin A Deficiency

Group	Subject		Normal	Mild	Moderate	Severe	Total
Group One	House Officers	Number	20	2	0	0	22
		Percentage	91	9	0	0	
Group Two	WPA Workers Medical Students Technicians Graduate Nurses	Number	98	42	7	2	149
		Percentage	65.8	28.2	4.6	1.4	
Group Three	Ambulatory Patients	Number	34	43	18	8	103
		Percentage	33.0	41.7	17.6	7.7	

Because of the excellent cooperation, reliable dietary history and the uniform nature of their diet, the members of group one were considered the control group. They were all healthy males varying from 24 to 35 years of age and free of serious intra-ocular disease.

The meals served in the doctors' dining room contained a varied and abundant supply of both vitamin A and carotene. Butter, milk and cream, in unlimited amounts, were served at every meal, eggs five times per week, cheese once per week, liver once per week, whipped cream on desserts weekly,

ice cream three times weekly, and pigmented (yellow or green) vegetables and fruit daily and often at each meal. From a theoretical consideration such a diet supplies more than the minimum amount of the vitamin needed.

With two exceptions, the photometer reading of each person in this group fell into a narrow range which was considered as normal. Each initial reading (after the five minute exposure to bright light) varied from wedge opacity four with a diaphragm aperture of 10 millimeters or less to a wedge opacity of five with a diaphragm aperture of 10 to 20 millimeters. After the 10 minute dark adaptation period, all readings were from the opacity six of the wedge with a small diaphragm aperture up to a wedge opacity seven with a large diaphragm aperture.

Several subjects took carotene daily, in addition to their diet, with no change in the photometer reading. This is in agreement with the work of Frandsen¹ who found that larger supplies of vitamin A than the body needs did not improve the visual acuity for dim vision once it reached a normal level. Repeated tests on a few of the subjects by different operators gave essentially the same photometer readings.

The two doctors in this group who failed to have a normal photometer reading fell into the mildly deficient group. One was trying to reduce weight and had deliberately avoided foods rich in vitamin A. The other had many food dislikes which caused him to avoid certain foods rich in vitamin A.

It was decided that any reading through wedge opacity four or five at the initial reading, and through wedge opacity six or seven after the 10 minute period would be considered as falling into the normal range and that person to be free from vitamin A deficiency. Table 2 contains representative photometer readings of persons who were considered to be receiving an adequate supply of vitamin A in their diet. Mild deficiency was

TABLE II

Representative Photometer Readings Obtained on Persons Receiving an Adequate Supply of Vitamin A

Subject	Initial Reading		Ten Minute Reading	
	Wedge	Diaphragm	Wedge	Diaphragm
House Officer	5	16	6	8
House Officer	5	10	6	10
Student	4	6	6	6
Technician	4	8	6	6
Student	4	14	7	20
Student	4	10	6	10
House Officer	4	4	6	6
Patient	4	4	6	4
House Officer	4	8	7	18
Visiting Physician	4	8	6	10
WPA Worker	4	4	6	6
Nurse	5	14	6	4

considered to be present when the initial reading was through wedge opacity three and final 10 minute reading through wedge opacity five, and moderate deficiency when the initial reading was through wedge opacity two and the final reading through wedge opacity three or four. Severe deficiency was considered to be present if the wedge opacities readings were less than the moderately deficient group.

It should be appreciated at this point that moderate and severe deficiency by this classification does not mean that the person has xerophthalmia or keratomalacia, but that they represent different degrees of hemeralopia. *Those falling into the severe deficiency group (as classified on the basis of this photometer test) represent the instances of vitamin A deficiency which are on the borderline of being detected by the usual clinical signs and symptoms*

Group two consisted of 149 subjects including WPA employees, medical students, technicians, and graduate nurses. All members of this group were healthy in the sense that they worked daily and had no specific complaints or diseases. Many of the WPA workers and medical students lived on surprisingly small incomes.

Compared to the control doctor group (with their adequate diet) the results here were entirely different, and probably representative of the general populace of poor financial circumstances.

Of 149 subjects tested, 98 (65.8 per cent) fell into the normal group (table 1). Of the rest, 42 (28.2 per cent) were mildly deficient in vitamin A, seven (4.6 per cent) moderately deficient, while two (1.4 per cent) were severely deficient.

Careful questioning of persons in the moderate or severe deficiency groups would often elicit complaints of some difficulty in vision in faint illumination. Several complained of difficulty in finding their way to a seat in a darkened cinema, trouble in driving an automobile at night or of being abnormally sensitive at night to glaring lights.

A study of the dietary habits of this group was interesting. The reasons for deficiency could usually be assigned to one of several obvious reasons. The financial reason was probably most important. A survey of the diet, consumed by control group one, which was shown to be adequate in vitamin A content, includes many expensive food substances. The best sources of vitamin A, such as butter, liver, cream, eggs, cheese and pigmented vegetables and fruits are distinctly expensive items. Persons who are forced to live on a frugal budget, whether they live at home or particularly if they eat in restaurants, can easily become deficient in vitamin A.

Peculiarities in food habits which cause foods rich in vitamin A or carotenoid substances to be avoided or disliked were responsible for several mild and moderate instances of deficiency. Another interesting group comprised those few persons (usually women) who because they feared obesity or were trying to reduce avoided many of the foods rich in vitamin A. The literature is replete with many papers emphasizing that a poorly

chosen reducing diet may cause any of several different deficiency syndromes. Vitamin A deficiency is no exception to this well known clinical observation. Such evidence indicates strongly the need for competent medical advice in the planning and supervision of any reducing regime.

Results secured by other workers, testing supposedly normal persons for vitamin A deficiency, can be compared to the results obtained in this group.

Jeans and Zentmire⁷² tested 404 children, ages ranging from six to 15 years, selected at random at four different places throughout the state of Iowa. Evidence of vitamin A deficiency was found in 26 per cent of the rural group and 53 per cent of the village group. In an urban group the proportion of deficiency for the higher economic level was 56 per cent, for a middle level 63 per cent and for a low economic level 79 per cent. The low figure for the rural district can be accounted for by the abundance of dairy and vegetable products in the diet of the average farmer. Where tested, 95 per cent of the deficient persons had a return of the photometer reading to normal and disappearance of the deficiency, following oral ingestion of either vitamin A or carotene concentrates. Sandler⁵ in studying a group of children living in an orphanage obtained results similar to the above.

Frandsen¹ and Edmund³ have published extensive studies on this subject and have tested many hundreds of subjects, including both children and adults. These investigators found that the percentage of deficiency for vitamin A varied for each group tested. In one group, 65 per cent of apparently healthy school children from Copenhagen were found to show deficiency. Children from orphanages were deficient in an even greater percentage of cases. Of groups of adults tested, the percentage of deficiency varied considerably from low to very high figures, in one instance reaching 90 per cent. Diet and economic conditions were the important factors in determining the degree of deficiency.

Park^{6,7} in testing groups of adults for vitamin A deficiency by the photometer method found it to be present in percentages comparable to those obtained by Frandsen¹ and Jeans and Zentmire⁷² for children. The rural group showed much less deficiency than the urban group. Women trying to reduce weight and persons who ate irregularly or improperly in restaurants were commonly found to be deficient. Park was able to cause the photometer reading to return to normal in practically every instance in a group of deficient persons who were given carotene orally.

These studies conducted in widely scattered locations (Denmark, Iowa, Chicago, Oklahoma and Boston) suggest the need for revision of our current conceptions of the prevalence of vitamin A deficiency which are based upon the old viewpoint, that marked hemeralopia, xerophthalmia or keratomalacia must be present before this diagnosis can be made. Hess and Kirby⁷³ in 1933, sent questionnaires to 50 leading ophthalmologists in this country and found that but few cases of severe night blindness or keratomalacia were observed. On the other hand evidence is accumulating to suggest that even clinically detectable night blindness is by no means rare if one carefully questions those persons whose photometer readings show marked impairment of dark adaptation. In the present series, several persons with such readings complained of difficulties referable to night blindness. Park⁶ found 12 persons who complained of night blindness. One can conclude that clinically detectable vitamin A deficiency, while un-

common, is not as rare as formerly believed. However, the evidence already available indicates strongly that sub-clinical degrees of vitamin A deficiency are very common.

This raises the question of the adequacy of the average American diet in regard to the entire vitamin content. McLester,⁷⁴ in discussing general malnutrition, points out that man's diet is seldom faulty in respect to one factor alone. Editorially, the *Journal of the American Medical Association*⁷⁵ comments: "The physician is chiefly interested in nutritional failure not because of its relation to scurvy, beri beri or any other well defined disease, but because it produces numberless vague poorly defined states of ill health. To prevent nutritional failure, the diet should be considered as a whole, and all essentials, whether vitamin, protein or mineral, should be accorded equal importance."

A situation, entirely comparable to the sub-clinical type of vitamin A deficiency, exists in this country in regard to vitamin C deficiency. Dall-dorf⁷⁶ remarks that, judged by clinical criteria, scurvy is uncommon in this country. An acquaintance with experimentally produced scurvy, however, indicates that various degrees of deficiency associated with a number of morbid changes can occur without classic symptoms or signs of the disease. Studies with the recently developed capillary fragility test⁷⁷ as a measure of sub-clinical scurvy and the direct determination of the amount of ascorbic acid in the blood plasma⁷⁸ suggest that sub-clinical degrees of scurvy are common.

Recent development of quantitative methods of determining other vitamin deficiencies has made the subject of sub-clinical deficiencies a practical and not a theoretical concept^{86, 87}. That sub-clinical degrees of deficiency for any or all of the vitamins exists seems very likely. The entire subject seems worthy of much consideration, and the future may change our present concept of what constitutes an adequate diet for the American people.

Group three comprised 103 ambulatory patients convalescing from the usual run of diseases which one finds on a general medical ward. No very sick or bed-ridden patients were tested, because the subject had to be well enough to walk to the dark room, sit on a stool for 20 minutes and otherwise cooperate in the test. With about a dozen exceptions, the tests were performed shortly before discharge of the patient. Patients with liver and gastrointestinal diseases were tested on admission if they were able to walk to the dark room. An ophthalmoscopic examination was done on each of these patients and only those with normal fundi and clear cornea and lens were used. It was found that cataracts, glaucoma, corneal opacities and various types of retinitis caused low photometer readings.

Thirty-four (33 per cent) of those tested showed no deficiency. While group three is small, they represented, on the whole, those with less serious illnesses, often of short duration.

Forty-three (41.7 per cent) were found to be mildly deficient in vitamin

A, 18 (17.6 per cent) moderately deficient, and eight (7.7 per cent) severely deficient

The sharp increase in the percentage of moderately and severely deficient persons in this group as compared to groups one and two can be explained as follows

(1) The persons in this group belong for the most part in the lower economic level

(2) Many had diseases which caused anorexia, vomiting, diarrhea or otherwise hindered the proper ingestion and absorption of the vitamin

(3) Many were entirely ignorant of what constituted an adequate diet

(4) Some had fever, infection or other disturbance which increased the metabolic need for vitamin A

(5) Several had liver damage which prevented the proper storage of vitamin A or the conversion of carotene to vitamin A

No attempt will be made to correlate vitamin A deficiency with all the diseases found in this group. The number of persons with each disease studied is too small for analysis. The study of a larger series, utilizing a portable photometer so that readings can be obtained from patients too sick to be moved, is at present under way and will be the subject of a later report. The results given here are really those of convalescent persons, and should not be taken as representative values of disease during its most severe manifestations. Undoubtedly, tests conducted on bed-ridden patients at the height of their illness will show an even greater degree of vitamin A deficiency than was present in members of group three.

Typical photometer readings obtained of persons from both groups two and three, who were considered to be either moderately or severely deficient, are tabulated in table 3. It can be readily seen that the photometer readings of this group are noticeably different from those of the control and mildly deficient group. Several persons in the moderately and severely deficient group had stigmata clinically suggesting vitamin A deficiency (i.e., dry skin, hyperkeratosis follicularis of the skin, dry conjunctivae or the subjective complaint of poor vision in dim illumination). Of the persons who saw the photometer light only through wedge opacity zero, one or two would usually complain of some manifestation of hemeralopia if carefully questioned. However, in most cases the degree of disability was not such as to cause them to seek medical advice specially for that complaint. In a group, at present under study, an attempt is being made to correlate photometer readings with these mild subjective and objective clinical evidences of vitamin A deficiency.

Frandsen¹ noted that persons with hemeralopia (as detected by tests for distinction power) often complained of palpitation, dry skin, dry mucous membranes, changes in sweat secretion, asthenopia, photophobia, *mouches volantes*, while the physical examination occasionally showed changes in the conjunctivae of a mild degree and dryness of the skin. Park⁷ observed

that persons with very low photometer readings showed one or more of the following general lack of vigor, easy fatigability, lack of luster of the cornea, nervous irritability, ptosis of eyelids and various visual difficulties including true night-blindness

These studies serve to indicate that while vitamin A deficiency rarely causes serious trouble, it may interfere with the efficient functioning of the body and cause many vague and annoying disturbances which detract from the desirable vim and vigor of life

TABLE III

Representative Photometer Readings Obtained on Persons Moderately and Severely Deficient in Vitamin A

Subject	Remarks	Initial Reading		Ten Minute Reading	
		Wedge	Diaphragm	Wedge	Diaphragm
Patient	Diabetes Mellitus	2	14	4	16
Patient	Hepatitis	0	20	1	14
Student	Disliked Many Foods	2	10	4	10
Patient	Active Malaria	3	10	5	10
Patient	Multiple Myeloma	2	12	4	12
Patient	Chronic Diarrhea	3	6	4	6
Patient	Bleeding Peptic Ulcer	3	4	4	6
WPA Worker	Chronic Sinusitis	3	10	5	8
Patient	Early Cirrhosis	3	8	4	8
Patient	Portal Cirrhosis	2	8	4	14
Technician	Poor Diet	2	10	4	12
Patient	Cancer of Colon—Diarrhea	1	16	2	8
Patient	Ulcerative Colitis	2	10	3	6
Patient	Obstructive Jaundice	2	6	3	8
Patient	Generalized Carcinomatosis	1	10	2	6
Orderly	Poor Diet and Food Dislikes	4	14	5	10
Patient	Chronic Alcoholism	2	6	4	10
Patient	Lobar Pneumonia	2	6	5	12
Patient	Catarrhal Jaundice	3	14	4	12
Student	Poor Diet	3	8	4	14

VITAMIN A DEFICIENCY DUE TO DISEASE

Evidence of vitamin A deficiency may develop even though the daily intake of the vitamin is theoretically sufficient to supply the needs of the body. Vitamin A and the carotenoid substances must not only enter the body, but must be completely absorbed from the gastrointestinal tract as well as changed and stored in the liver before being ready for use by the body.

On a theoretical basis it can be predicted, and from the literature can be gathered much evidence to show, that vomiting, various types of gastrointestinal and gastro-colic fistulae, changes in the gastrointestinal mucosa, lack of pancreatic secretion and chronic diarrheas can all hinder the proper absorption of vitamin A and carotene^{6, 7, 17, 20, 21}. Evidence is also available

to show that there may be a differential absorption of pure vitamin A and carotene. Under certain conditions one may be absorbed where the other is not¹¹. Where such pathological conditions exist it is necessary to increase the intake of vitamin A many times over normal to compensate for the inefficient absorption.

Three persons who were ambulatory and had diarrhea of at least six months' duration were tested with the photometer. The results are included among the results tabulated in table 3. Two were treated for four weeks with 10,000 units (U S P) of carotene daily with no improvement in the photometer readings. Park⁶ reports that where diarrhea existed in his patients no improvement was noted in the photometer readings if the usual oral dose of carotene was utilized. These results suggest that the dose of vitamin A in the presence of poor absorption must either be increased enormously or some vitamin A preparation given parenterally. Parenteral injections have been shown to be effective both experimentally⁹ and in humans^{1, 79}.

Since the liver serves to store vitamin A, release it according to the body needs and convert carotene to vitamin A, one would expect liver damage to cause vitamin A deficiency. It has long been known that liver disease could cause even clinically detectable vitamin A deficiency^{79, 80}. Examination of livers post-mortem for the vitamin A content showed that livers with diffuse damage, caused by fibrosis, inflammation or tumor, had marked reduction in the amount of vitamin A stored¹³.

Photometer tests, both in the present series and in cases reported by Park⁶ and others,¹¹ show that practically every patient with liver disease gave low readings. Of six persons with liver disease, who were able to be ambulatory, all gave low readings on the Birch-Hirschfeld photometer. The readings of four of these cases are included in table 3. The diagnoses included toxic hepatitis, catarrhal jaundice and portal cirrhosis. Two of these were treated with carotene with little or no change in the photometer reading. One woman with hepatitis took carotene, 20,000 units (U S P) daily, for five weeks. In spite of this large dose, the photometer readings did not improve until the jaundice cleared, when within one week a change was noted. The patient was discharged before the study could be completed. Parenteral injection of vitamin A has been reported as successful in liver disease⁷⁹. Since the liver serves to convert carotene to vitamin A, one would expect on theoretical grounds that vitamin A concentrates would be a better source of vitamin A than carotene. However, no data are available to show this.

Aside from absorption and storage, metabolic changes influence the amount of vitamin A needed by the body. Fever,⁸ infection¹⁷ and pregnancy¹⁹ have all been shown to increase the need for vitamin A. Wendt¹⁸ has shown in experimental animals that the presence in the blood stream of an increased amount of thyroxin diminished the vitamin A reserve. In

addition he was able to show that a high basal metabolic rate in humans increased the need for vitamin A. Not enough data have been collected yet to show what the photometer readings would be in persons with hyperthyroidism.

Park⁶ has noted in his series of cases that persons with fever and infections of various types often had low photometer readings. Edmund¹⁹ believes that pregnant women not only have a greater metabolic need for vitamin A but that gastrointestinal absorption of this vitamin is less efficient during pregnancy.

It is evident from the data already on hand that the subject of vitamin A deficiency in various diseases is extremely important and its significance only beginning to be realized.

RESULTS OF THERAPY OF VITAMIN A DEFICIENCY

Belief in the specificity of essential hemeralopia as a measure of vitamin A deficiency (whether detected clinically or by means of a photometer or other instrument) rests on the prompt disappearance of both the subjective and objective manifestations following vitamin A therapy.

Empirically it has been known since the time of Hippocrates² that certain types of hemeralopia would disappear when treated with liver. However, it remained for Bloch⁸⁰ and Blegvad⁷⁰ to correlate the lack of vitamin with essential hemeralopia, xerophthalmia, xerosis conjunctivae and keratomalacia.

Spence⁸⁰ noted that gross hemeralopia improved in three to five days and entirely disappeared in from seven to ten days when cod-liver oil and butter were given in large amounts. Aykroyd⁸¹ and others^{1, 81} have reported similar results.

Every investigator who has studied vitamin A deficiency by means of a photometer or determination of distinction power has noted a return to normal readings after a period of vitamin A ingestion. Frandsen¹ and Edmund³ used cod-liver or halibut-liver oil concentrates and found that most readings became normal within three weeks. Jeans and Zentmire⁴ used three teaspoonfuls of cod-liver oil daily and found that the recovery period varied from four days to six weeks, with an average of about 12 days. Later these same workers⁷² noted that similar results could also be obtained with either cod-liver concentrates or carotene. Park⁶ used carotene in oil (daily dose equivalent to 15 teaspoonfuls of cod-liver oil) and found that the photometer readings returned to normal in from six to 41 days.

The most striking proof that the vitamin A supply of the body controls the photometer reading and distinction power was presented by Edmund¹⁹. This investigator found that a single intra-muscular injection of a vitamin A preparation (40,000 I U per c c) brought about the disappearance of

hemeralopia and an improvement in the readings in the course of from seven to ten minutes

In the present study, 14 of the persons in group two (healthy active adults) who showed low photometer readings were treated with vitamin concentrates with no change in their diet. Each person received daily a carotene capsule⁷ containing 10,000 U S P units of vitamin A activity. Each person was retested at the end of two, three and four weeks on the therapy. The results are tabulated in table 4. With one exception (where it took one month), the photometer reading returned to the normal range after either two or three weeks. Those with very low photometer readings noted a subjective improvement in the ability to see in the dark. One man believed his furuncles cleared for the first time in years. Several persons thought they had more "pep" than usual. Such subjective improvements are hard to evaluate and must be studied on a larger group with appropriate controls.

Of particular interest were three young women who ate at the same boarding house. All showed low photometer readings. The diet was adequate in calories but poor in vitamin A rich food. With no change in diet, one woman had a normal photometer reading after taking carotene for several weeks, while no change was noted in the others.

The results obtained here, plus data collected from the literature, suggest that 5,000 to 10,000 U S P units of vitamin A, whether taken as cod-liver oil, vitamin A concentrates or carotene, will abolish all subjective and objective evidence of vitamin A deficiency even if the diet remains inadequate. However, if any disturbance is present which increases the metabolic need for vitamin A or hinders the absorption or storage, then far greater doses would be needed. It may also be necessary to resort to parenteral therapy.

Since many of the foods rich in vitamin A are relatively expensive, it is suggested that it would be cheaper in many instances to add some vitamin A preparation to the diet rather than attempt to increase the vitamin intake by adding foods rich in vitamin A. This applies in particular to institutions with limited budgets and persons of poor financial means.

A word of caution concerning the excessive use of carotene would be of value. If carotene is absorbed from the intestinal tract faster than the liver can convert and store it, the surplus may be stored in the body tissues and cause a yellow color (carotinemia) to appear. This condition may resemble jaundice, but is, however, neither a disease nor dangerous, and promptly disappears when the intake of carotene is curtailed. None of the subjects in this study developed carotinemia although carotene of dose 10,000 U S P units was taken daily for periods as long as six weeks. Both Park⁶ and, Sandler⁵ had instances of carotinemia in their series when the dose of carotene was pushed above this level.

* The carotene used in this study was generously supplied by the SMA Corporation of Cleveland, Ohio.

TABLE IV

Photometer Readings on Normal Persons Deficient in Vitamin A and Results after Vitamin A Therapy

Subject	Remarks	Photometer Reading before Vitamin A Therapy						Length of Time Vitamin A Therapy Was Given	Photometer Reading after Vitamin A Therapy			
		Initial Reading		Ten Minute Reading		Initial Reading			Ten Minute Reading			
		Wedge	Diaphragm	Wedge	Diaphragm	Wedge	Diaphragm		Wedge	Diaphragm		
Student 27	Ate in restaurant Poor diet for financial reasons	3	8	4	14			2 weeks	4	10	6	8
Student 24	Ate at home—Poor choice of foods	3	12	5	14			2 weeks	5	8	7	14
Student 27	Ate at home—Avoided foods rich in vitamin A	2	14	4	12			2 weeks	5	10	7	10
Technician 21	Disliked all foods rich in vita- min A	4	12	4	8			1 month	4	14	5	6
Nurse 26	Trying to lose weight Avoided vitamin rich foods	3	14	5	16			3 weeks	4	12	6	10
Student 24	Financial reasons—poor diet	3	14	5	10			3 weeks	4	10	7	10
Technician 22	Poor diet for financial reasons	3	16	5	14			2 weeks	4	12	6	10
WPA Worker 34	Poor diet—Lack of money	3	20	4	14			3 weeks	3	2	6	18
Technician 20	Poor diet—Trying to lose weight	3	12	4	14			2 weeks	4	10	6	12
Nurse 29	Trying to lose weight—Avoided vitamin rich foods	3	14	5	16			2 weeks	4	12	7	14
Student 28	Ate in restaurant Poor diet	3	14	5	12			2 weeks	4	8	6	6
WPA Worker 37	Poor diet—Ate at home	3	14	5	10			2 weeks	4	12	6	14
Technician 23	Poor diet—Financial reasons	2	8	4	6			2 weeks	3	6	5	10
Student 26	Poor diet—Financial reasons	3	16	4	8			2 weeks	4	10	6	14

SUMMARY

1 The literature dealing with the physiology, biochemistry, pathology and clinical aspects of vitamin A deficiency is reviewed

2 Night blindness (hemeralopia), in the absence of intra-ocular disease, is the earliest and most constant manifestation of vitamin A deficiency in adults

3 In adults, night blindness may exist for years as the only manifestation of vitamin A deficiency

4 Night blindness is associated with certain objective data which can be measured by means of special procedures. These serve as a quantitative estimate of the degrees of vitamin A deficiency and are particularly valuable in that they can detect deficiency long before it becomes clinically manifest

5 The results of studying 274 adults by means of a Birch-Hirschfeld visual photometer and data collected from the literature show that mild to moderate degrees of vitamin A deficiency are common among many supposedly healthy adults

6 Financial reasons, peculiarities in choice of foods, ignorance of a proper diet and a desire to reduce weight, were among the factors leading to deficiency

7 Vitamin A deficiency may occur even if the amount ingested daily is theoretically adequate if any condition is present which (a) increases the metabolic need for vitamin A (fever, infection, elevated basal metabolic rate, rapid growth and pregnancy), (b) interferes with the proper absorption from the gastrointestinal tract, or (c) interferes with the conversion of carotene or storage of vitamin A in the liver

8 Vitamin A deficiency is probably a constant feature of liver disease, and does not respond to the usual oral doses of vitamin A

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CRYSTALLINE INSULIN¹

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It is now 14 years since insulin was made available to the medical profession and the results of a vast experience with its effects are now at hand. About two years ago, a modified insulin, protamine insulin, was offered to the medical profession. One of the most interesting revelations that came with this new insulin was the limitations of the old insulin. When reports began coming in on the new insulin, we came to realize how many insulin-treated diabetics in the hands of highly experienced workers were not under good control at all. This admission should have its sobering influence and its good effects.

At this point, let it be said that the newer insulins are nothing other than the original insulin which has been more or less modified. It is as though the vehicle for insulin has been changed and the new vehicles are such that the insulin molecule which they contain is absorbed gradually, and therefore acts more slowly.

CRYSTALLINE INSULIN

One of these newer insulins is crystalline insulin. Insulin was first crystallized by John Jacob Abel of Johns Hopkins University. It is the purest known form of insulin substance. Chemically, crystalline insulin is a complex protein obtained as the end-product of the bovine pancreas. It is a complex molecule which can be broken down into such amino-acids as lysine, cystine, histidine, arginine, leucine, tyrosine, phenyl-alanine, glutamic acid and proline. While up to the present time no one of these amino-acid fractions or any known combination of them has been found to produce the physiological effect of the whole crystalline insulin molecule, it is said to have been the hope of Abel that this complex molecule might be so altered, or combined in such a way as to leave it unaffected by the gastric and intestinal juices. When that is attained, oral administration of insulin may be realized and a great want will be met. Until that is achieved, insulin must be used by the injection method.

Insulin is an amphoteric substance. It has an iso-electric point and above and below this point there is a zone in which its solubility is variable. Beyond that zone the solubility of insulin is rapid and complete. The upper limits of this zone lie usually at a pH of 6.0 to 6.2. Dr. Melville Sayhoun of Detroit has, however, prepared a new crystalline insulin whose solubility is complete only at a pH of 6.4 to 7.0. Its advantages may be stated in simple terms. An insulin of greater alkalinity is absorbed more slowly by the tissues and blood and this in turn slows down the glycolytic effects of the insulin molecule.

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This new crystalline insulin was released for clinical study about six months ago and we have been working with it since that time. Throughout our studies with this new preparation, we aimed at determining its clinical value on the basis of its effects in comparison with results already obtainable with standard insulin and protamine insulin.

AIMS IN INSULIN THERAPY

The physician treating a diabetic aims at the avoidance of hyperglycemia and hypoglycemia. He desires to accomplish this with a minimum number of injections, for reasons both of convenience and of economy to the patient. These aims will be attained when we have an insulin that will have a positive effect in lowering the blood sugar and one that will do it without getting beyond our control. The ideal insulin and the ideal dosage should stop short of producing insulin reaction or insulin shock, and its action should continue throughout the entire post-cibal absorptive period.

METHOD OF STUDY

Our patients ordinarily receive a liberal carbohydrate and low fat diet, with a commensurate amount of insulin. The only change that we made in the routine of these patients was to substitute crystalline insulin for the standard or protamine insulin which they had been taking. On the appointed day, hourly blood sugars were taken from 8 a.m. to 9 p.m. and hourly specimens of urine were obtained. In the following charts, the solid line represents the level of blood sugar while on standard insulin, the broken line represents the level of blood sugar after the patient had been taking crystalline insulin for a period of three to 14 days. As nearly as possible, all conditions were made the same for the hospital and ambulatory patients.

GLYCOLYTIC EFFECT OF CRYSTALLINE INSULIN

To what extent crystalline insulin can accomplish this may be seen in the following examples.

Case 1 A diabetic patient was stabilized on diet alone and was nearly sugar normal about the eighth day in the hospital. He had not received insulin. An hourly blood sugar curve was made on the eighth day (chart 1). On the eleventh day, he was given 15 units of crystalline insulin at 8 a.m. and the hourly blood sugar curve repeated. The glycolytic value of the crystalline insulin is reflected in the relative position of the two curves on the chart. A further index of the relative values of these two curves is obtained by adding the milligrams blood sugar of every hour. Without insulin the total value is 3168 mg. On the day crystalline insulin was given, the total value of the curve was 2877 mg. It is very evident that the blood sugar was markedly lower after the crystalline insulin, the first and only dose the patient received. These are advantages in taking a patient having a moderate hyperglycemia and glycosuria. In such a case the work done by the insulin is measured with greater certainty.

A glance at this chart further shows that the immediate effect of crystalline insulin was to lower the blood sugar from 180 mg to 77 mg in three hours. It should also be noted that the blood sugar trend for the following nine hours was kept within bounds and that is important. Had we given this patient a larger dose, we may rightly assume that the blood sugar would have reached lower levels.

Case 2 Mr T had been using standard insulin for three years and was under satisfactory control. With standard insulin the sum total of his hourly blood sugar

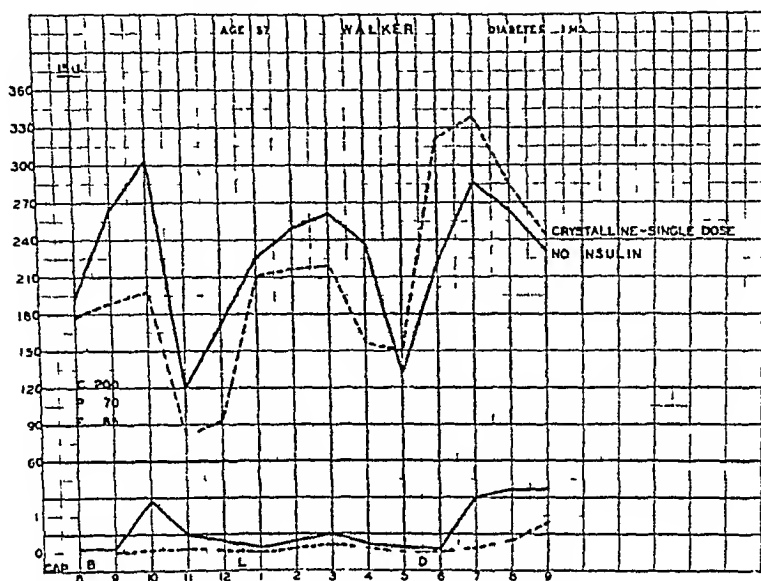


CHART 1 Hourly blood sugar curves. Solid line no insulin. Broken line crystalline insulin. Glycosuria depicted in lower curves.

curve was 3512 mg. After he had been on the same dose of crystalline insulin, which was substituted for his regular insulin, for seven days, an hourly curve for that day (chart 2) showed a total of 2660 mg. It will be noted that the fluctuations under crystalline insulin were smaller and the curve was comparatively level. It is interesting to note here that the insulins were given before the evening meal and while his blood sugar was quite high in the morning, it fell progressively during the day, regardless of his breakfast and luncheon having been taken without insulin. In part this may have been due to insulin, his own or that which was given him once daily.

CRYSTALLINE INSULIN SERIES

We repeated these experiments in a group of 21 diabetics, making daily curves while the patient was on standard insulin and again after a period of 3 to 14 days or longer on crystalline insulin. Out of these, we found that 12 patients showed a distinctly lower curve with crystalline insulin, while 9 showed a lower curve with standard insulin. In the 12 cases, crystalline insulin lowered the blood sugar to a greater extent and the entire curve remained at a more even level.

The following charts are typical cases which reacted well with crystalline insulin.

TOTAL EFFECT OF CRYSTALLINE INSULIN

We constructed curves based on the average of blood sugar levels for the entire series of cases, as they were affected by both standard insulin and crystalline insulin (chart 8). In this study, we found that in the entire series of 21 cases, standard insulin kept the blood sugar at a lower level than crystalline insulin for a period of 36 units of time, while the same dosage of crystalline insulin kept the blood sugar at a lower level than the standard insulin did for a period of 125 units of time.

The deduction from these observations leads us to the belief that unit for unit, crystalline insulin accomplishes more than standard insulin.

EFFECT ON URINE SUGAR

Along with the hourly blood sugar, we also obtained hourly specimens of urine in these patients. Charts 1 and 3 are examples of the relative effect of crystalline and standard insulins on the total glucose metabolism. In a way, quantitative glycosuria reflects the glucose utilization even more completely than hourly blood sugars.

DURATION OF EFFECT A SINGLE DOSE

In analyzing our curves, we find a marked difference in the length of time that a single dose of crystalline insulin affects the blood sugar curve in different patients. In the last analysis, this may represent the rate of insulin absorption. In our experience it was evident that in juvenile diabetics, absorption must be more rapid or factors yet unknown are at work.

Our observations reveal that whereas in the middle-aged or older diabetics crystalline insulin seemed to lower the blood sugar progressively for a period of 72 hours, in the young diabetics the downward curve was nearer 42 hours' duration. The cause of this is not always easy to estimate in a patient having three meals daily and more than one dose of insulin per day. Whether this variability in effect is due to rate of absorption or insulin sensitivity and insulin insensitiveness, is an unsettled question.

CRYSTALLINE INSULIN FAILURES

There was one group of five cases in which the crystalline insulin curve was definitely not as good as the regular insulin curve. Of these patients, three were middle-aged diabetics and two were juvenile diabetics. In one of these young diabetics we repeated the experiment and found that standard insulin was better than either crystalline insulin or protamine insulin, as charts 9 and 10 will show.

INSULIN REACTION—SHOCK

In going over the blood sugar curves and histories of the entire series, we found that insulin reactions and shock were four times as frequent in the

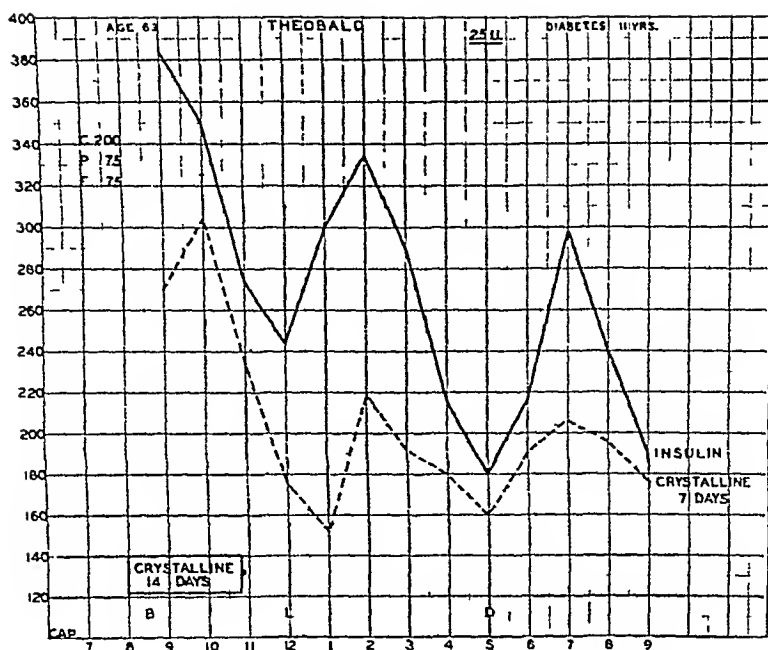


CHART 2 Hourly blood sugar curves After 14 days on crystalline insulin, the morning blood sugar was 130 mg

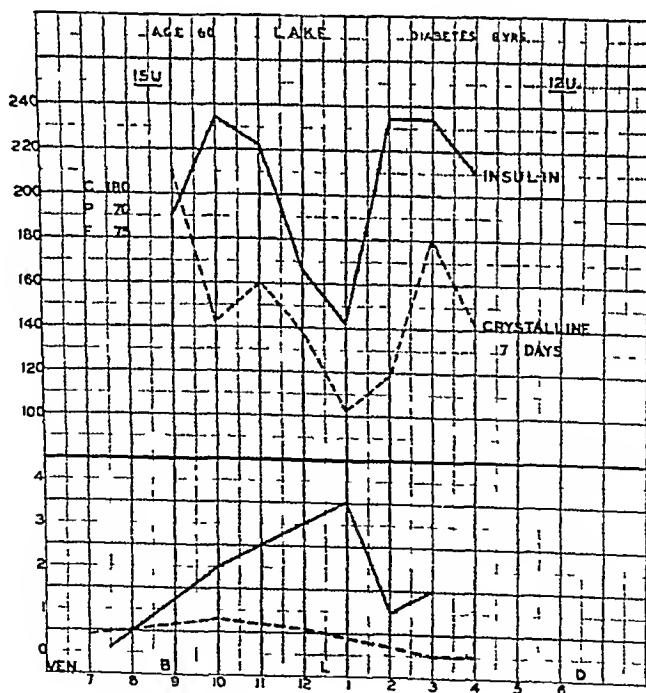


CHART 3 Blood sugar curve on standard and on crystalline insulin Note curve of glycosuria, below

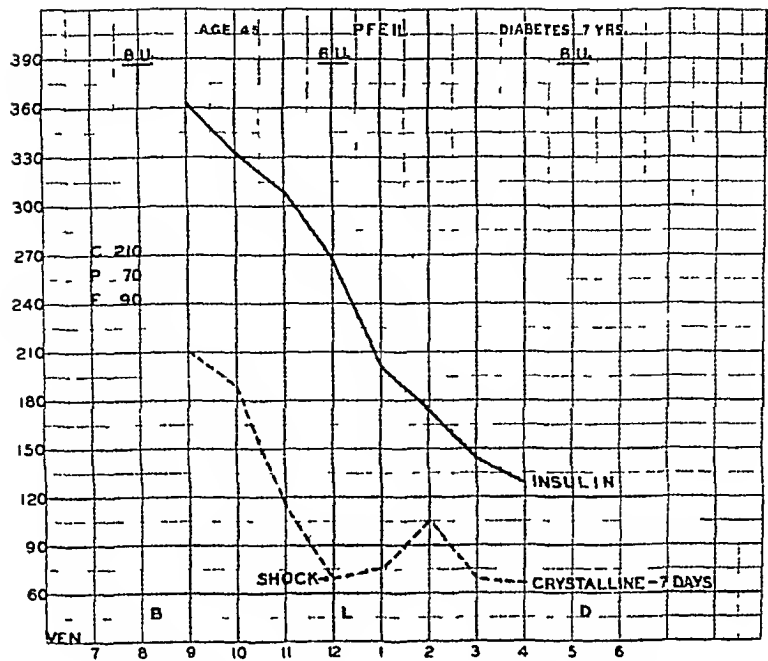


CHART 4 Blood sugar curves on standard and on crystalline insulin

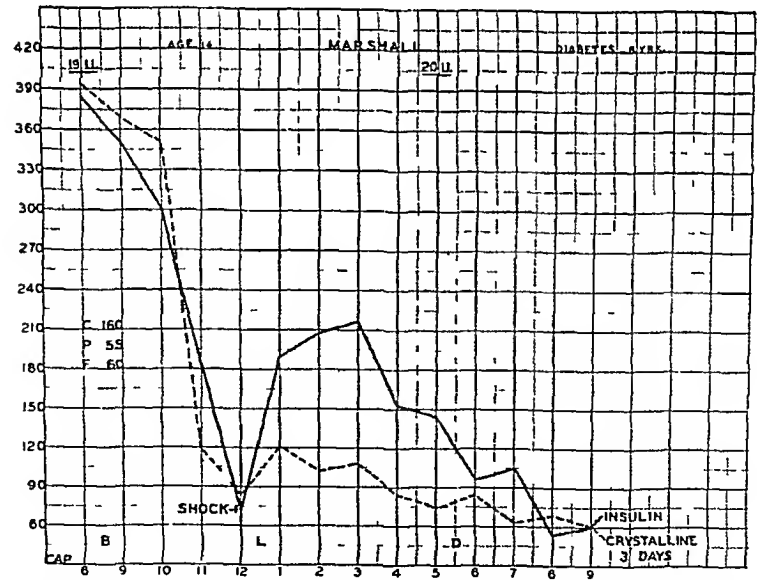


CHART 5 Blood sugar curves on standard and on crystalline insulin

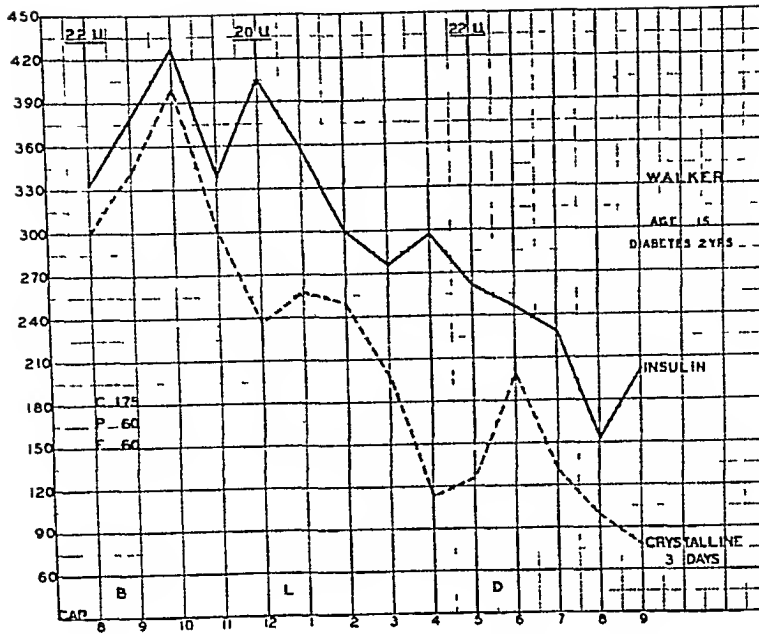


CHART 6 Blood sugar curves on standard and on crystalline insulin Blood sugars by capillary method

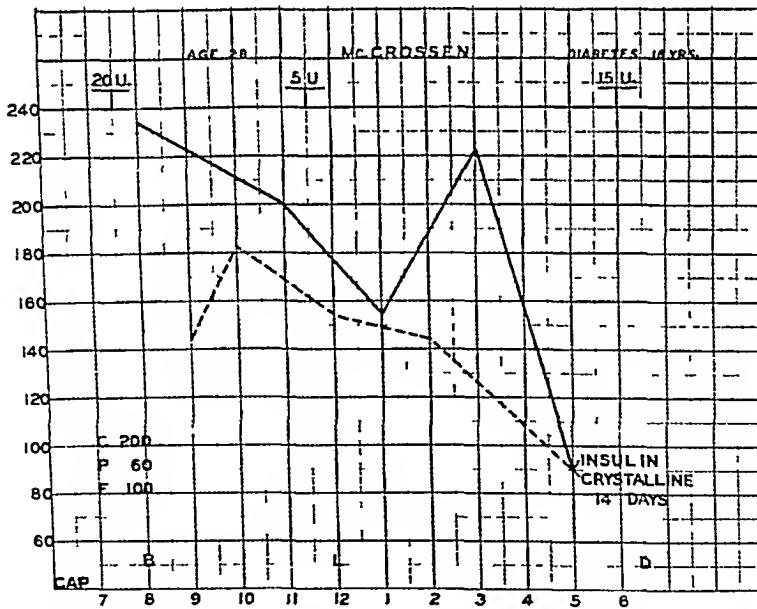


CHART 7 Blood sugar curves on standard and on crystalline insulin Blood sugars by capillary method

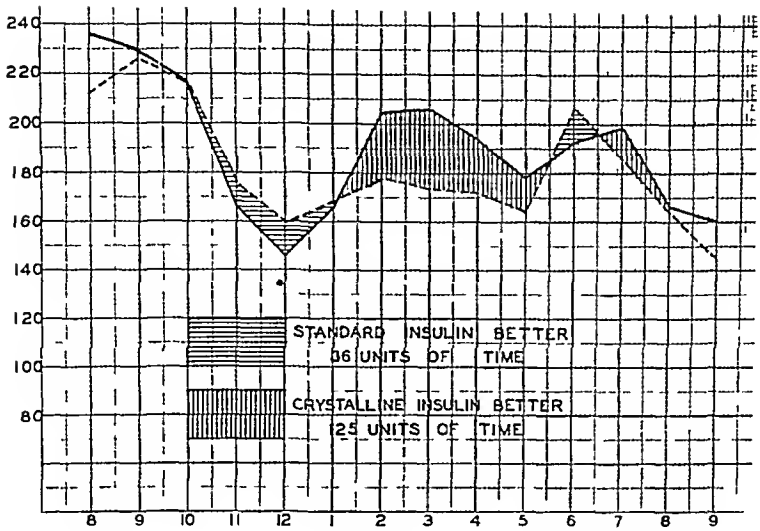


CHART 8 Glycolytic effects of crystalline and standard insulins in 21 cases

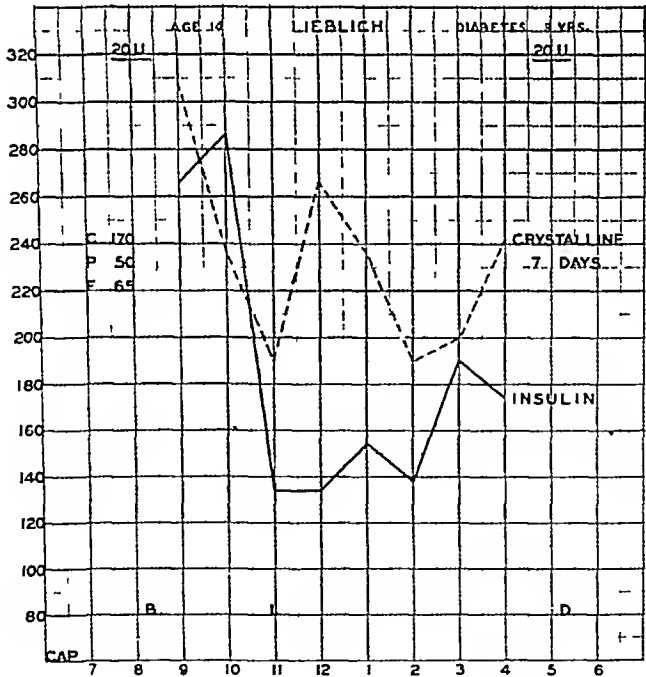


CHART 9

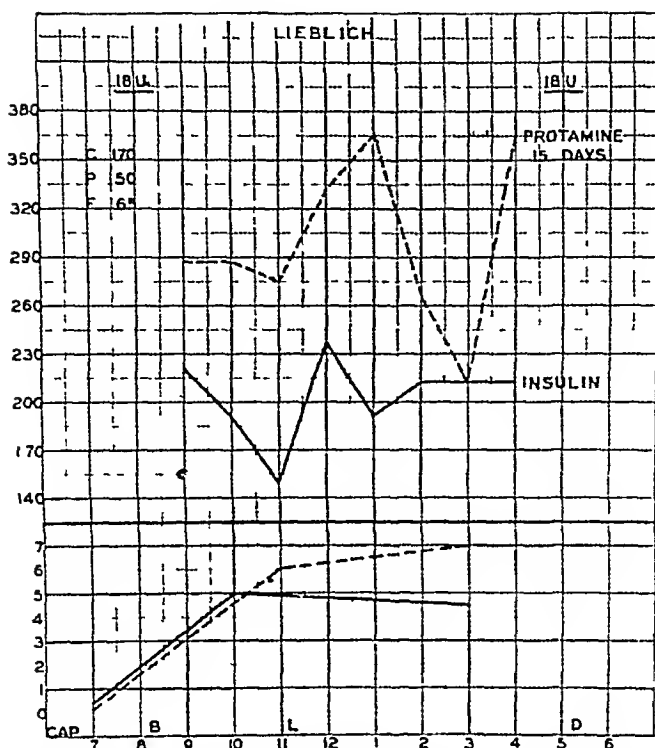


CHART 10 In this patient, standard insulin was distinctly more effective than crystalline or protamine insulin

standard insulin periods as in the crystalline insulin periods. It was noteworthy that in crystalline insulin cases, when the blood sugar was in the 50 mg zone at which time reactions usually begin to manifest themselves, these patients failed to show the usual symptoms.

SUMMARY AND CONCLUSIONS

Up to the present time, we have found no disadvantages whatever in the use of crystalline insulin, either in its administration or in its effects. Its sugar reducing value by every means that we could determine was actually greater than regular insulin in 12 out of 21 cases. It was less effective in 9 out of 21 cases. The absorption time of crystalline insulin is longer and its glycolytic effects are of greater duration. Insulin reactions or insulin shock occurred only one-fourth as often as when standard insulin was used. Because of its slower action and lessened tendency to produce shock, larger doses may be used to reduce the number of doses per day.

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LOBAR PNEUMONIA, AN ANALYSIS OF 1298 CASES *

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It is our purpose to analyze the cases of lobar pneumonia in patients admitted to the Buffalo City Hospital from January 1, 1927, to December 31, 1935. During that period 106,374 patients were admitted to the hospital, and of that number 1298, or 1.2 per cent were considered to have lobar pneumonia. Only those cases were included which represented unquestionably typical lobar pneumonia after critical evaluation of clinical records, radiographic findings and postmortem records. Roentgenograms were made in 40 per cent of the cases in this series, while necropsies were performed on 37 per cent of those patients dying of the disease. Of the 1298 patients, 787 recovered, while 511 died, a mortality of 38.5 per cent. It should be stated that in 32 per cent of the fatal cases, the patients died within 12 hours after admission, while nine were moribund upon arrival. If these patients are excluded, the corrected mortality is 37.8 per cent. Even this figure might be considered excessive by some authorities. However, Cecil¹ in a recent report on the death rate in pneumococcal pneumonia states that the death rate varies considerably with the class of the patient studied, being lowest in private practice, somewhat higher in hospitals treating the better class, and highest in hospitals treating purely indigent cases. Thus, the mortality at the Rockefeller Hospital is 19.5 per cent, and at the Bellevue Hospital 35.8 per cent.†

Despite the fact that pneumonia has dropped from second place in 1900 to sixth in 1934, it is still one of the leading causes of death. Metropolitan Life Insurance statistics² indicate that the 1934 death rate in pneumonia was 79.4 per 100,000 population. According to the New York State Department of Health,³ pneumonia causes more loss of life in that state than any other single communicable disease and is exceeded as a cause of death only by heart disease and cancer. The annual loss of life from this cause in New York State alone is estimated at 12,000.

Mortality varies in some degree from year to year, month to month, and markedly so in respect to age incidence and the type of invading organisms.

This yearly variation with its concomitant mortality is clearly depicted in figure 1 and it is apparent that in the majority of years, the mortality rate paralleled the incidence. During the nine year period the lowest incidence was in 1932, while the highest was in 1929.

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† The Buffalo City Hospital in many respects resembles the Bellevue Hospital, being a municipal general hospital which receives and treats chiefly indigent patients suffering from all types of disease.

An investigation of the incidence of lobar pneumonia for the same period in Buffalo, N. Y.,⁴ confirmed this observation. At the same time, reports gathered from various cities in the United States by the Metropolitan Life Insurance Company² revealed that this high pneumonia incidence prevailed

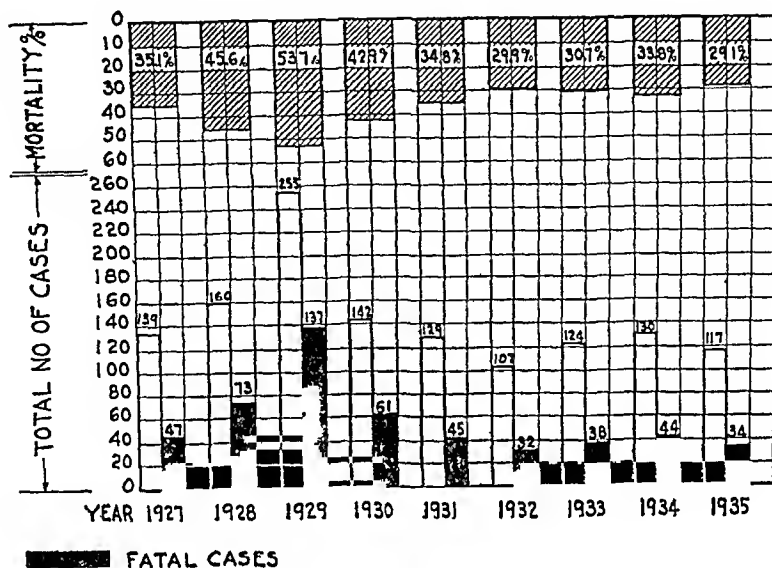


FIG 1 Yearly incidence and mortality

throughout the country. It was evident from a study of the yearly snowfall and mean temperatures in Buffalo,⁵ that 1929 was not particularly remarkable from this standpoint. Analysis of typing in the present series

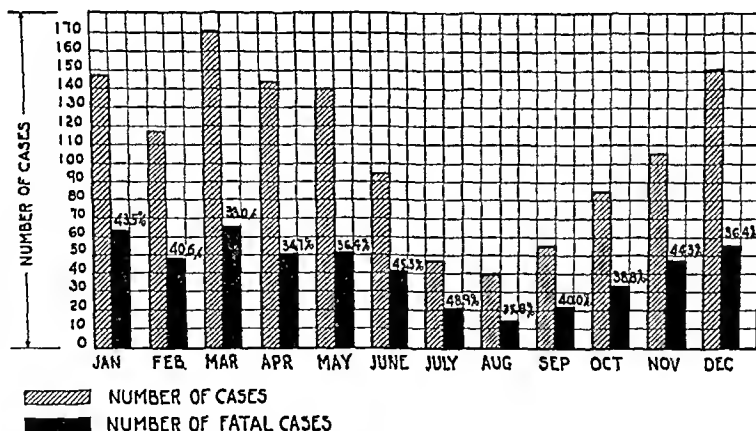


FIG 2 Monthly incidence of pneumonia and mortality For period 1927-1935 inclusive

failed to show any predominant type during that year. No explanation is offered except that the country at large was the victim of a mild epidemic.

It is generally true that lobar pneumonia occurs chiefly during the cold winter months, December through March, but figure 2 indicates quite defi-

nitely that April and May on the average produce approximately as many cases as all of the winter months except March. It is also important to note that though the incidence was lowest in the summer months, the mortality rate in summer was actually higher than in the corresponding winter months. An effort was made to determine if meteorological conditions in any way influenced the incidence of pneumonia. Although no absolute relationship could be traced, the highest incidence peaks occurred during months in which precipitation and snowfall were greatest, and the average mean temperature low. This is shown in figure 3.

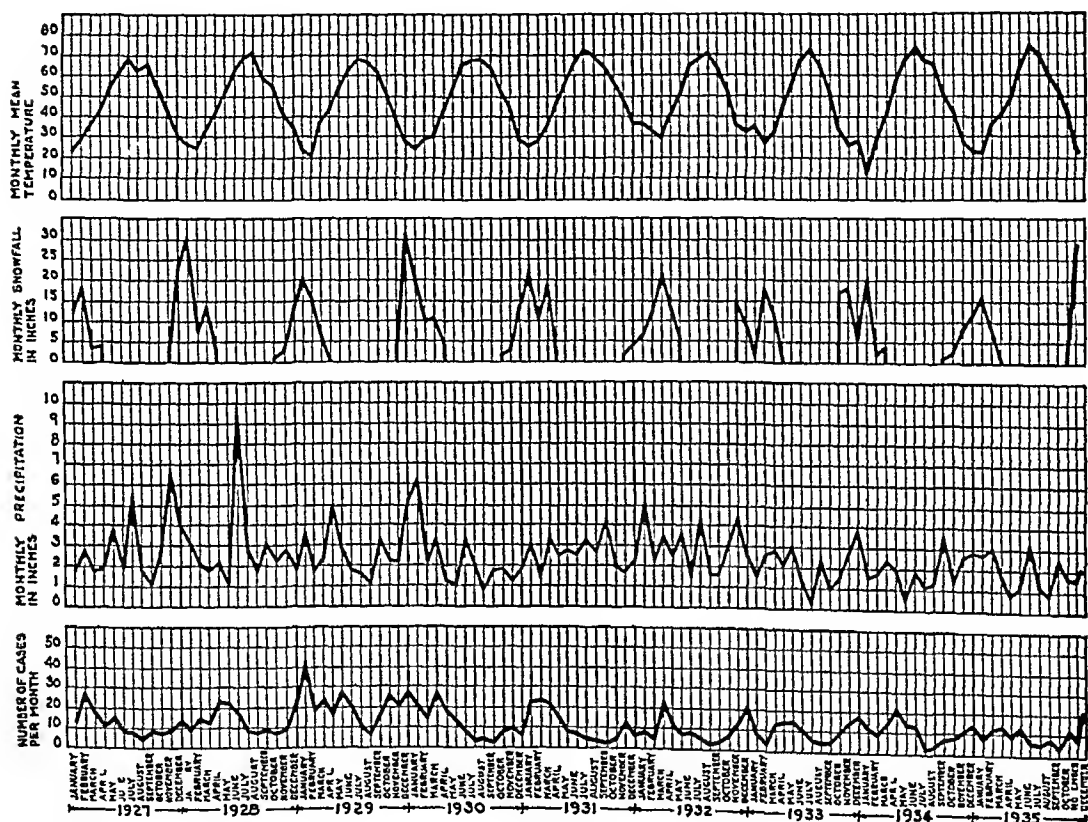


FIG 3 Incidence of lobar pneumonia in relation to precipitation, snowfall and mean monthly temperature

SEX

It is generally believed that lobar pneumonia, like most serious diseases, occurs more often in men than in women. In this series of 1298 patients, 969 patients were men and 329 patients were women, a ratio of about three to one (figure 4). The mortality among women was 31.9 per cent, while in the men, the mortality was 41.9 per cent or exactly 10 per cent higher. This greater incidence and the increased death rate in men most likely was based on such factors as occupation with its subsequent exposure, mode of living, and alcoholic indulgence.

COLOR

Negroes in Buffalo comprise 2.4 per cent of the total population. In this series 23.2 per cent of the patients were colored, 2.2 per cent were American Indians, and the remainder, 74.5 per cent, were white people. Despite the fact that colored races are generally much more susceptible to respiratory ailments, including tuberculosis, the mortality was higher in the white patients than that in either the negro or Indian patients. This is graphically shown in figure 4.

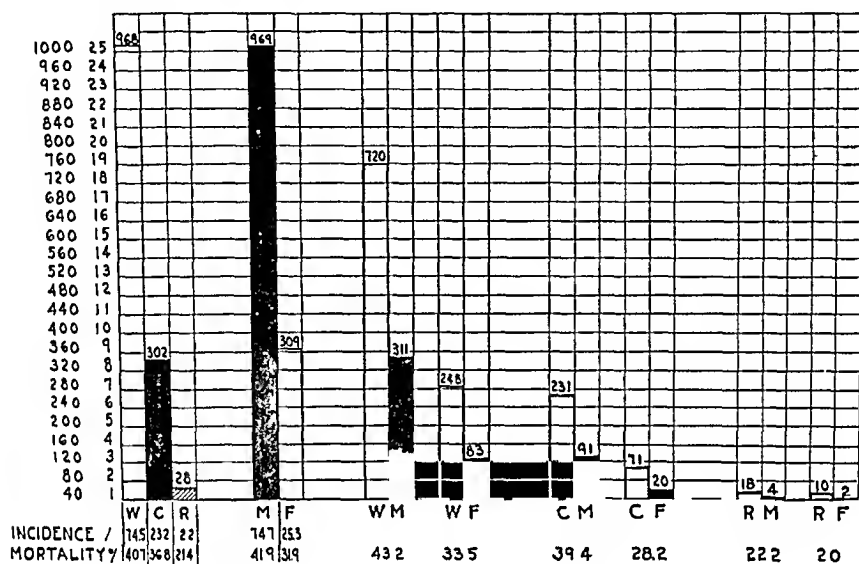


FIG. 4. Relationship of color and sex to incidence and mortality.

W—White
C—Colored
R—Indian

M—Male
F—Female

AGE

Figure 5 demonstrates the effect of age upon the incidence and the death rate. It is clear that lobar pneumonia is a very serious disease in infants under one year. As children become older the mortality rate gradually declines until the age period of five to ten is reached when it strikes its lowest ebb (9.5 per cent). From that age until senility, the death rate progressively increases in a direct proportion to the age.

The highest incidence periods seem to lie between 20 and 50. Fifty-three per cent of the patients who developed the disease were within this age period. The single decade showing the highest incidence occurred between the ages of 30 and 40.

SYMPTOMS

The onset of lobar pneumonia is usually described as abrupt. Musser⁶ states that antecedent respiratory infection had occurred in slightly over 40

per cent of the Rockefeller Hospital patients. Sudden onset in 58.1 per cent of our patients was followed by a mortality of 31.7 per cent, while in 41.9 per cent who started gradually the mortality was 29 per cent. If the assumption is true that those patients who experienced a gradual onset were in reality the victims of a previous respiratory infection, it is evident that the so-called common cold was actually the precursor of lobar pneumonia in 42 per cent of the cases. Whether or not the type of onset bore any prognostic relation to the mortality is not demonstrated.

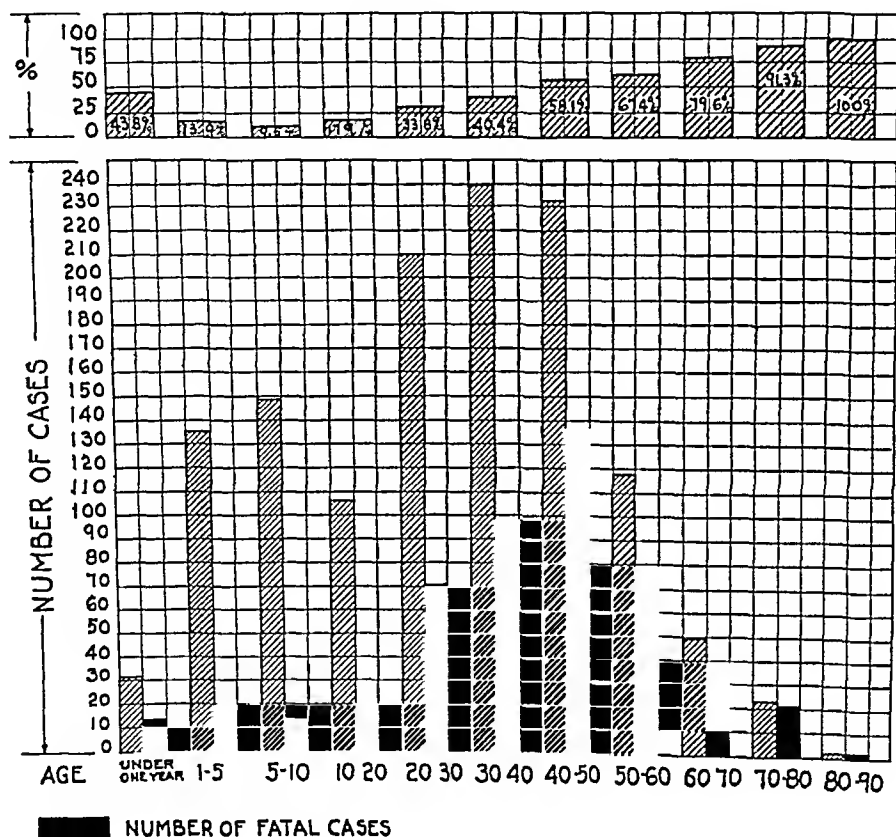


FIG 5 Age incidence and mortality

The common cardinal symptoms were considered, such as cough, pain in the chest, chills, dyspnea, and hemoptysis, along with the complicating symptoms, cyanosis, ileus and hiccough. The relative incidence of the various symptoms is shown graphically in figure 6, together with the mortality of the aforementioned complicating symptoms. Although most textbooks list the chill as the most common characteristic symptom, figure 6 clearly indicates that the dry hacking cough was the most constant symptom in this series. Obviously this symptom, because of its frequent occurrence in practically all respiratory diseases, is not pathognomonic of lobar pneumonia, but combined with the other symptoms shown in the table, produces valuable

clinical leads. Pleural pain, which is generally regarded by pathologists as the result of stretching of adhesions, was the next most common symptom, occurring in 61.1 per cent of the patients, and even though second in frequency was still nearly twice as common as chill. The latter symptom, typical chill, occurred in only 33.2 per cent of the patients although more complained of mild chilly sensations. It is interesting to note that Reginald Fitz,⁷ in Peter Bent Brigham Hospital, found only a slightly higher percentage (37 per cent). While the respiratory rate was increased in practically every instance, some patients complained of marked difficulty in breathing. This dyspnea was present in 22.2 per cent. Hemoptysis, the fifth most common symptom in frequency, occurred in only 21.5 per cent of the patients. It should be mentioned that only manifest bloody sputum was considered hemoptysis, blood-streaked or blood-flecked sputum was excluded.

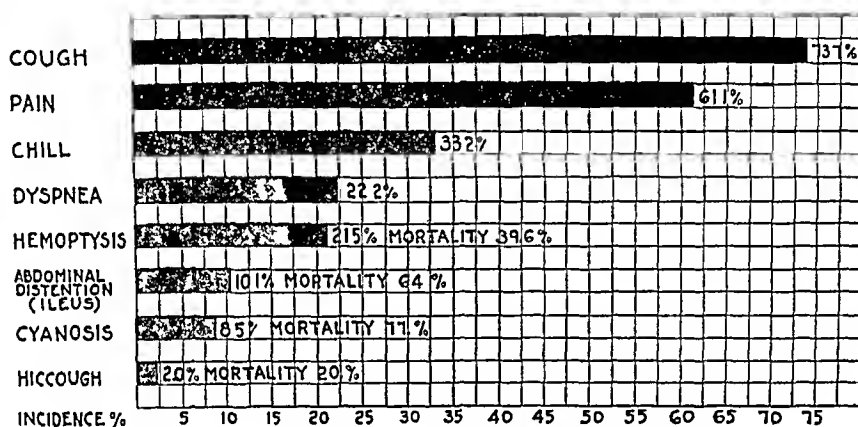


FIG 6 Incidence of symptoms in lobar pneumonia

Cyanosis, ileus and hiccough, though usually regarded as signs, are included in this discussion as complicating symptoms because the latter two frequently occur late in the course of the disease. Our criterion of cyanosis was definite blueness of the lips, fingernails and face, and did not include transient or mild duskiess. It is apparent from figure 6 that although of rather infrequent occurrence, it was an ominous sign.

Marked abdominal distention as a result of ileus is also a serious complicating symptom. It was found in only 10.1 per cent of the patients but carried with it a mortality of 64 per cent. This symptom is probably an expression of profound toxemia upon the sympathetic nerve endings controlling the small intestine.

Hiccough, a rather rare symptom, occurred in only 2 per cent of the cases with a 20 per cent mortality.

From time immemorial lobar pneumonia has been considered the one disease that terminates abruptly by crisis. Cecil,⁸ on the contrary, feels that the majority of cases decline gradually by lysis. Only 54.5 per cent of our

patients who recovered had a sudden fall in temperature, in the remainder the temperature fell gradually by lysis

At this point it seems advisable to recapitulate with an evaluation of symptoms according to the commonly accepted pathogenesis of the disease. Blake and Cecil⁹ have demonstrated that the primary pathologic process in the development of pneumonia is a penetration of the walls of the larger bronchi by the pneumococci. This process in addition to the tracheo-bronchial infection gives origin to the dry hacking cough which was not only the earliest but the most frequently observed symptom. Following the penetration of the bronchi, the organisms pass along the lymphatics of the fibrous septa in a rapid centrifugal direction until the periphery is attained. In the wake of this process the alveoli are reached and ultimately perforated by the pneumococci. This sequence makes it apparent that the exudative process which results in consolidation really starts at the hilus and proceeds peripherally. At the same time the foregoing statement in a measure explains why pleural pain was the second most common symptom. This conception of the pathogenesis of pneumonia may serve as an explanation for the fact that a chill occasionally is observed after the occurrence of cough and pleural pain, and in this series occurred in only one-third of the patients. Both dyspnea and cyanosis are expressions of anoxemia which many authorities feel is due to fluid on the inside of alveoli preventing the diffusion of gases. It seems likely that dyspnea is the result of a moderate anoxemia, while cyanosis, with a mortality of 77 per cent, is a manifestation of grave oxygen lack.

At the same time, it seems quite apparent that the symptoms should be the earliest manifestation of the pneumonic process and precede the development of outspoken signs of clinical consolidation by a matter of hours varying from 12 to 48. We noted this frequently.

LOBAR INVOLVEMENT

Comparisons were made in this study in an effort to determine the relative incidence and mortality of individual lobar involvement, multi-lobe involvement, and the various frequency of upper and lower lobe solidification. This is clearly portrayed by figure 7. Right-sided involvement, including single and multiple lobe consolidation, occurred in 754 patients (58.1 per cent) with 300 deaths (39.8 per cent). Left-sided lesions, considered in a similar fashion, occurred in 462 patients (35.6 per cent), with 162 deaths (35.1 per cent). It is apparent that lobar pneumonia was much more frequent in the right lung, but the mortality considered as a whole was only slightly higher in this location. A comparison of the frequency of involvement of the upper lobes as opposed to the lower lobes reveals that the right and left upper lobes were individually affected in 18.5 per cent of the patients (mortality 29.6 per cent) while the lower lobes were individually attacked in 48.1 per cent of the patients (mortality 33.8 per cent). This

indicates that individually the right lower and the left lower lobes were attacked $2\frac{1}{2}$ times as often as the upper lobes. The ratio is practically the same as that found by Warr and Alperin¹¹ who reported the lower lobes involved twice as often as the uppers.

Similar comparative studies of lobar involvement with relative frequency and mortality rates are described by many writers. Cecil⁸ found the right side involved 666 times and the left 598 times. In his series, the right lower and the left lower lobes were involved in about equal frequency of all single lobar lesions. Right and left lower lobe consolidation was by far

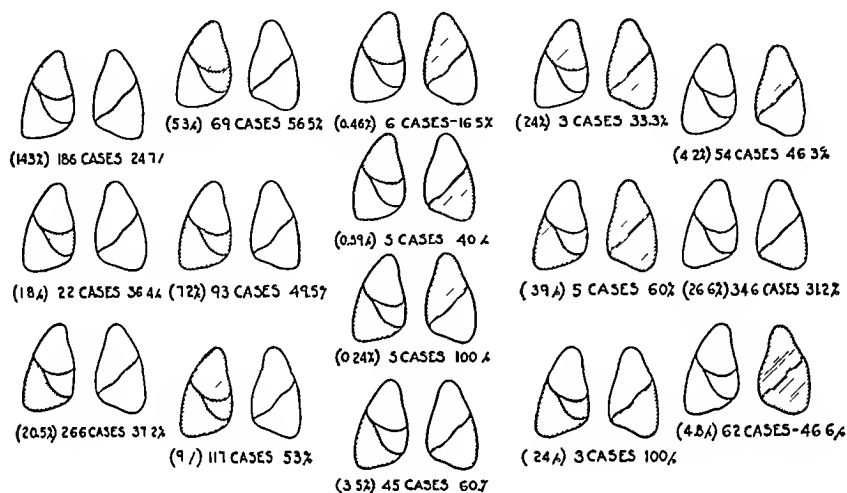


FIG. 7. Lobar involvement in 1298 cases of lobar pneumonia with percentage of mortality.

Note: Figures in parentheses indicate percentage of incidence of various lobar involvement.

Consolidation is indicated by cross hatching.

- Rt Upper and lower—1 case—0 per cent
- Rt Lung and left upper—2 cases—50 per cent
- Rt Lung and left lower—2 cases—50 per cent
- Rt Upper and middle and left upper—2 cases—100 per cent
- Rt Upper and middle and left lower—1 case—100 per cent
- Rt Upper and lower and left upper—1 case—100 per cent
- Rt Upper and lower and left lower—1 case—100 per cent
- Rt Middle and left lower—2 cases—50 per cent
- Rt Upper and middle and entire left—1 case—100 per cent

the commonest bilobar combination. His conclusions were that the seriousness of the disease varied directly with the number of lobes involved. This is in agreement with McCrae¹⁰ who, quoting statistics from 100 autopsies performed at the Montreal General Hospital, reported right-sided lesions in 51 and left-sided lesions in 32. Both lungs were involved in 17. In 29 cases the entire lung was involved, and in 34 merely the lower lobe was affected. The upper lobes alone were affected 13 times. When double, the lower lobes were usually consolidated together, but in three instances the lower lobe in one lung and the upper lobe in the other were solidified. Only in three were both upper lobes affected.

Just why the lower lobes are more often affected than the upper lobes is speculative. If it is assumed that approximately 40 per cent of the patients developing lobar pneumonia have previous respiratory infection, and that lobar pneumonia, as Coryllos and Birnbaum¹² have shown, is essentially a pneumococcal atelectasis due to a bronchial obstruction from a catarrhal plug, the anatomy of the bronchial tree with the right and left bronchus practically continuous with the main bronchus, makes it appear quite logical that the plug should eventually locate in these lower bronchial passages.

SINGLE LOBAR INVOLVEMENT

In discussing monolobar consolidation, it is apparent from figure 7 that the left lower stood out as the most frequently involved lobe, occurring in slightly more than one-quarter of the cases in the entire series (346 cases). Despite the marked frequency of involvement in this particular lobe the mortality was only 31.2 per cent, considerably less than the adjoining upper lobe or the opposite lower lobe. The next most frequent single lobe affected was the right lower which occurred in 20.5 per cent with a mortality of 37.2 per cent. The right upper lobe was third in frequency with an incidence of 14.3 per cent. The left upper lobe was involved in only 4.2 per cent, but was associated with a high mortality (46.3 per cent). Peculiarly enough, although right-sided lesions are almost twice as frequent as left-sided lesions, and although the middle lobe in many cases is almost an integral part of the right upper, this lobe was involved in only 1.8 per cent with a mortality of 36.4 per cent.

MULTILOBAR AND BILATERAL LOBAR INVOLVEMENT

While Harlow Brooks¹³ concluded from his series of 200 autopsied cases that the extent of lung involvement was but of minor value as a prognostic factor in death in lobar pneumonia, many observers, including the authors, have felt that it is one of the important contributory influences producing a fatal outcome.

The following table tends to corroborate this latter viewpoint, and indicates quite distinctly that mortality in multiple lobar involvement is directly proportionate to the number of lobes involved.

It is interesting to note that pneumonia in more than one lobe occurred

TABLE I
Extent of Lobe Involvement in 1298 Cases

Number of Lobes Involved	Total Cases	Fatal Cases	Per cent Mortality
One	874	286	32.7
Two	286	148	51.7
Three	133	74	55.6
Four	5	3	60.0

in about one-third of the entire series, which is slightly higher than the percentage found by Warr and Alperin¹¹ who found multiple lobar involvement in only one-quarter of their series. These authors also stated the mortality was higher when the disease was bilateral than when two or more lobes of one lung were involved.

J A Ryle¹⁴ of Guys' Hospital, writing on the prognosis of lobar pneumonia, is of the same opinion and lists excessive bilateral involvement as the most serious of unfavorable factors in determining prognosis.

Table 2 substantiates the contention that bilateral involvement materially increases the mortality rate and adds to the seriousness of the prognosis.

TABLE II
Bilateral Bilobar Involvement

Lobes Involved	Total Cases	Fatal Cases	Per cent Mortality
Both lowers	45	27	60.0
Both uppers	6	1	16.5
Left lower and right upper	5	2	40.0
Left upper and right lower	3	3	100.0
Right middle and left lower	2	1	50.0
Total	61	34	Av. 55.7

ALCOHOL

Evidence of alcoholic poisoning, manifested chiefly by delirium tremens, was present in 73 patients (figure 8). All were men and 58, or nearly 80

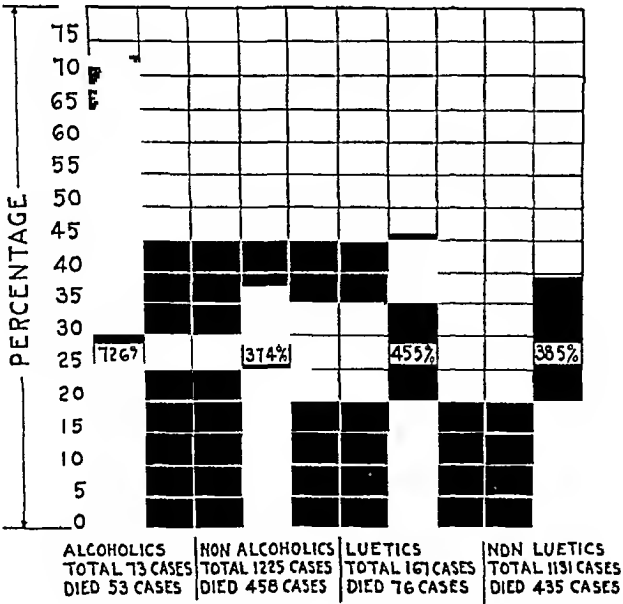


FIG 8 Per cent of mortality in alcoholics and luetics as compared to non-alcoholics and non-luetics

per cent, were white. Fifty-three patients died with a resultant mortality of 72.6 per cent. This mortality is almost double that of the non-alcoholic patients. One might expect a higher percentage of alcoholic patients in a large series such as this, but it should be remembered Harlow Brooks¹³ found histories of alcoholism in only five of his 200 postmortem cases. Undoubtedly there are many more patients who were alcoholics of some degree but were not the severe chronic drinkers who might be expected to develop delirium tremens.

Some observers have felt that chronic alcoholism predisposes to certain lobe involvement. In the present series 22 per cent of the total number of alcoholics developed a right lower lobe pneumonia, while in 18 per cent it was in the left lower lobe. This is interesting as left lower lobe pneumonia occurred in 27 per cent of the total number of patients, while right lower lobe consolidation occurred in 21 per cent of the total number. Although the percentage difference is relatively small, it seems that alcoholics developed processes in the right lower lobe more often than in any other single lobe. No explanation is offered for this coincidental finding.

RELATIONSHIP TO SYPHILIS

Of our 1298 patients, 167 or 12.8 per cent had a positive Wassermann reaction, and of this number, 76 died and 91 recovered, a mortality of 45.5 per cent. This figure is 7 per cent higher than the mortality for the whole series or for the non-luetic group (see figure 8). Seventy-two (43.1 per cent) patients were white, 93 (55.7 per cent) were colored, and two (1.2 per cent) were Indians. The large number of colored patients does not explain this increased mortality as it was shown in figure 4 that the mortality actually is higher in the white race.

It was also thought that possibly fatalities occurred here because of increased age and the presence of late cardiovascular lues. Investigation revealed that these fatal cases were quite evenly distributed throughout the age groups. Only four of the fatal cases showed gross luetic meso-aortitis on postmortem examination. The relationship to typing was inconclusive.

Again a survey of various lobar involvements was undertaken in the 167 patients with lobar pneumonia and syphilis to establish whether any particular lobar predilection existed. The lower lobes were attacked in 41 per cent of the cases, the uppers in only 16.2 per cent, and the middle lobe in only 1.8 per cent. The right lower and left lower lobes were involved almost equally.

The problem of delayed resolution or unresolved pneumonia was also considered in its relationship to syphilis. This complication was relatively uncommon in this series as it occurred in only 27 patients (1.8 per cent). Of these, only four (14.8 per cent) had a positive Wassermann test. These observations are essentially the same as those made by Weinstein and Goodman¹⁵ (Johns Hopkins Hospital) who considered that delay in resolution

TABLE III
Complications

	Total Cases	Incidence	Recovered	Died	Mortality %	Type I			Mortality %	Type II			Type III			Mortality %	Type IV			Mortality %	Untyped			Mortality %	Strep			Mortality %
						R	D	T		R	D	T	R	D	T		R	D	T		R	D	T		R	D	T	
Empyema	120	9.3%	16	74	61.7	19	8	27	29.6	5	2	7	1	1	2	28.6	5	1	6	16.7	16	61	77	73	0	1	1	100
Pleural effusion	62	4.8%	40	22	35.5	4	2	6	33.3	2	2	4	1	1	2	50	3	0	5	0	28	17	45	37.8				
Otitis media	48	3.6%	44	4	8.3	4	0	4	0	2	0	2	2	1	3	33.3	0	0	0	0	36	3	39	7.7				
Chronic fibrous pleurisy	37	2.8%	35	2	5.4	6	0	6	0	5	1	6	1	0	1	16.7	1	0	5	0	18	1	19	5.3				
Pericarditis	28	2.1%	4	24	85.7	1	5	6	83.3	1	0	1	0	0	0	0	5	0	3	100	2	16	18	88.9				
Unresolved pneumonia	24	1.8%	21	3	12.5	3	0	3	0	4	0	4	0	0	0	0	1	0	1	0	13	3	16	18.8				
Lung abscess	16	1.2%	5	11	68.8	0	1	1	100	1	0	2	0	0	0	100	0	1	3	0	4	0	13	69.2				
Meningitis	13	1.0%	0	13	100	0	0	0	0	0	0	1	1	1	1	100	0	0	0	0	0	6	100					
Bronchiectasis	14	1.08%	2	12	85.7	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	2	11	13	84.6				
Tuberculosis	10	7.7%	4	6	60	1	1	2	50	1	0	1	0	0	0	0	1	0	1	0	1	5	6	83.3				
Jaundice	10	7.7%	7	3	70	2	0	2	100	0	0	0	0	1	1	100	0	1	1	100	1	5	6	83.3				
Peritonitis	3	2.3%	0	3	100	0	1	1	100	0	0	0	0	0	0	0	0	0	0	0	0	1	1	100				
Atelectasis	3	2.3%	2	1	33.3	1	0	1	0	1	0	1	0	0	0	0	0	0	0	0	0	1	1	100				
Arthritis	2	1.5%	2	0	50	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	100				
Cellulitis	2	1.5%	2	0	0	1	0	1	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0				
Pleuro pericarditis	1	0.77%	0	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
Abscess rt arm	1	0.77%	1	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	100				
Pyoarthritis	1	0.77%	0	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0				
Pyelonephritis	1	0.77%	0	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	1	100	0	0	0	0				
Cellulitis of scrotum and penis	1	0.77%	0	1	100	0	0	0	0	0	0	0	0	0	0	0	0	0	1	100	0	0	0	0				
Left parotitis	1	0.77%	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	100				
Totals	395		211	184		44	19	63		22	8	30	5	5	10		19	11	30		128	141	269					

of the pneumonic process occurred almost as frequently in the non-syphilitics as in the syphilitics

LEUKOCYTE COUNT

The total leukocyte count has long been regarded as an index to prognosis in lobar pneumonia. It is usually conceded that a good leukocytic response indicates that the patient's fighting forces are mobilized to combat the invader. Total leukocyte studies were made on slightly more than 70 per cent of the patients in the present analysis. Figure 9 demonstrates quite clearly that the optimum total leukocyte count to ensure a good prognosis lies between 30,000 and 40,000. It is also evident that as the total leukocyte

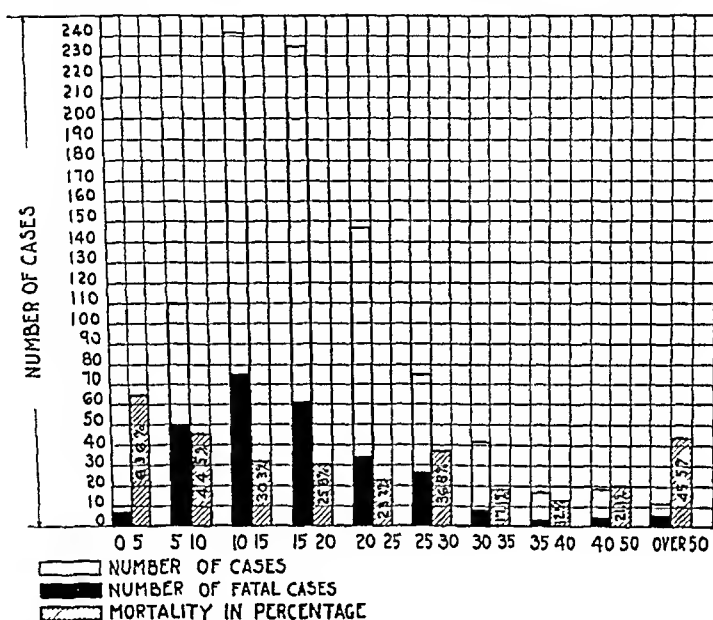


FIG 9 Total leukocyte count in thousands

count decreases from 10,000 downward, the mortality increases in a direct proportion. This is to be expected because diminished resisting forces permit the infection to overwhelm the patient. At the same time, as the total count increases over 50,000, the mortality rate progressively increases. This might be explained by the probability that even though the bone marrow was actively responding to the infection, the toxemia was so profound that death ensued as a result of its degenerating effect upon the heart, higher brain centers and periphero-vasomotor nerve endings.

During the past few years considerable attention has been directed to the differential count as advocated by Schilling. It is generally accepted that the so-called "shift to the left" with an increasing output of young forms indicates a doubtful prognosis. In this survey, total polymorphonuclear leukocyte counts were analyzed, without deriving evidence therefrom,

Schilling counts were performed only during the years 1934 and 1935 so that conclusions are unwarranted at this time

TYPING

The type of pneumococcus was ascertained in about one-quarter, 313, of these patients. This rather small number was due to the fact that the procedure was relatively difficult and expensive during the years preceding 1934, but with the advent of the Neufeld method in 1935, this difficulty has obviously been overcome. However, it is interesting to note (figure 10) that

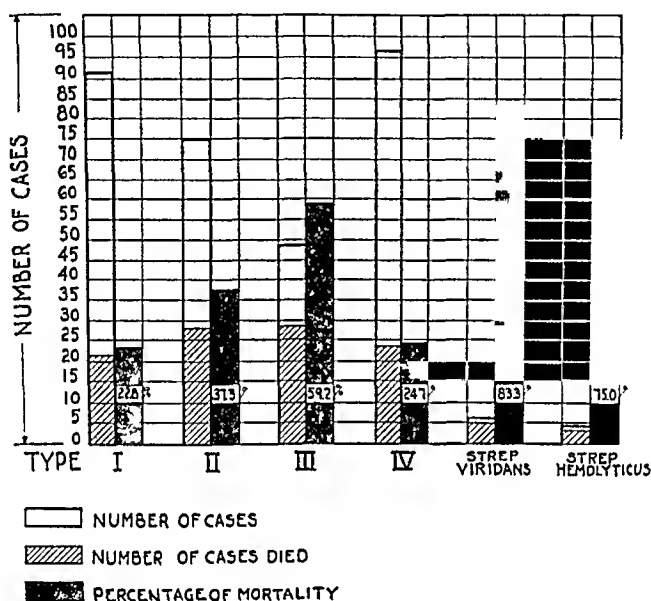


Fig 10 Typing and percentage of mortality

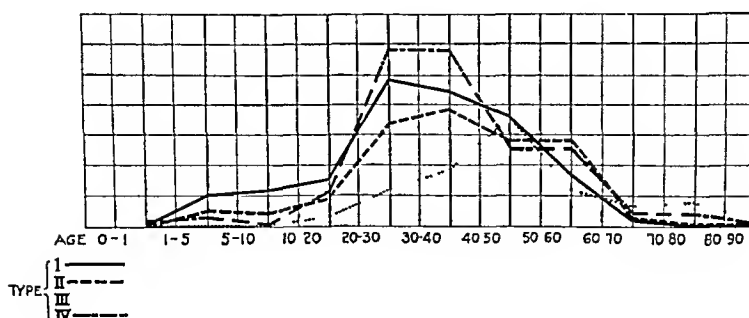


FIG 11 Relationship of age incidence to type

the incidence is greatest of types I and IV and lowest of type III. At the same time, the mortality rate of type III was approximately twice that of any of the other types, or equivalent to the mortality of any two other types. These observations are not new and have been previously stated by Cecil.⁸

and other authors. It also can be seen from figure 2 that type I and to some extent type II were most common in the patients under 40, while type III occurred more frequently than any other type in patients over 40. This partially accounts for its high mortality rate and also for its relatively low incidence.

It also will be seen from table 3 that type I was the most frequent producer of complications, particularly empyema. On the contrary, type III seldom or rarely produced complications. This paucity was probably related to the fact that nearly 60 per cent of these patients died in the acute phase of the disease before complications usually occur.

COMPLICATIONS

Empyema, in our experience, was the most common complication. It is to be remembered that empyema is always a complication and never a sequel. One hundred and twenty patients (93 per cent) developed pus in the pleural space. This high incidence requires a few words of explanation. In 69 patients (57.5 per cent) the diagnosis of empyema was tentatively made by clinical examination and confirmed by paracentesis. Of these, 46 recovered and 23 died (mortality rate 33.3 per cent). In 13 of the other 51 cases diagnosed at autopsy, there was a rather massive empyema, while in 38 there was present only a purulent exudate on the pleura. The latter finding was designated fibrino-purulent pleurisy, which may be classified as empyema because this type of pleuritis is in reality a localized or loculated empyema. Therefore, in 82 patients there were rather large collections of pus in the pleural space, while 38 others merely developed a purulent appearance of the pleura itself. Many writers feel that if all fatal cases of pneumonia were autopsied, the recognized percentage of empyema would be considerably higher, and it appears that this series supports that viewpoint. However, if the cases showing only fibrinopurulent pleurisy were excluded, the incidence of empyema is 6.3 per cent, which is approximately the percentage found by Cecil⁸ and his co-workers. McCrae¹⁰ basing his statistics on the Johns Hopkin's series, found only 3.6 per cent, while Musser⁶ estimates the incidence as being between 3 and 5 per cent. Warr and Alperin,¹¹ in their large series of 2,039 cases, found an empyema incidence of only 2.6 per cent. It is quite likely that 7 or 8 per cent would be a more accurate figure if all fatal cases of lobar pneumonia were investigated post mortem. Then, too, a great deal depends on whether one is to include rather minute collections of pus in the pleural space as empyema. The mortality rate in empyema in this series was 62 per cent.

Pleural effusion was the second most frequent complication, occurring in 62 patients (4.8 per cent). This figure was considerably higher than that found by Warr and Alperin,¹¹ who recorded only eight pleural effusions in 2,039 lobar pneumonias. Joules¹⁶ reported only five effusions in his series of 496 cases. Both of these figures seem low, if it is borne in mind

that in our series only 22 of the 62 effusions were discovered by postmortem examinations. The remaining 40 diagnoses of pleural effusion were made by clinical examination, roentgenographic studies and confirmed by paracentesis. In all probability most lobar pneumonia is accompanied by slight pleural effusions which are not diagnosed due to lack of sufficient quantity or hesitancy and fear of aspiration.

Next in frequency was otitis media. This complication occurred in 48 patients (3.6 per cent). It was by far the major complication in childhood. Forty-two of the 48 cases occurred under the age of 10. This complication can be considered relatively mild in severity as the mortality was only 8 per cent, or less than the general mortality for the age group from 1 to 10 years.

Chronic fibrous pleurisy also was a frequent complication but it is such a natural pathological sequela to the pneumonic process that further discussion is unnecessary.

Pericarditis was next in frequency occurring in 28 patients (2.1 per cent). The mortality was 85.7 per cent, making this complication one of the gravest. The majority of cases occurred in left-sided lesions which was to be expected inasmuch as pleuritis, pleuro-pericarditis and visceral pericarditis is the usual pathologic sequence.

Unresolved pneumonia or delayed resolution occurred in only 1.8 per cent of the patients. The relationship to syphilis has been discussed. Tuberculosis has been thought to be responsible for many unresolved processes, but in this survey positive evidence of superimposed tuberculosis was rare, as will be brought out later.

Lung abscess was also a relatively rare sequel, developing in only 16 patients (1.2 per cent). This incidence was slightly higher than the Bellevue series of 2122 cases, where only 9 cases were observed. The mortality was exceedingly high, ending fatally in 11 (69 per cent).

Meningitis, the most severe of all complications or sequelae, occurred in 13 patients (1 per cent) terminating fatally in all cases. This outcome must be expected as meningeal involvement is practically always the result of an overwhelming pneumococcal septicemia.

Other complications, such as bronchiectasis, tuberculosis, jaundice and peritonitis, occurred rather infrequently. Bronchiectasis was present in 14 cases (1.8 per cent), 12 of which were discovered post mortem. Apparently it is extremely rare in patients recovering from the disease. Ten patients subsequently developed tuberculosis. It is, therefore, suggested that series showing a higher incidence of tuberculosis possibly include acute pneumonic forms of tuberculosis. Jaundice also occurred in 10 cases with a mortality of 70 per cent. The mechanism of jaundice in lobar pneumonia is rather obscure. Some observers feel that it is chiefly hemolytic, while others attribute it to parenchymatous hepatic degeneration. It is probably a combination of the two processes and in either event is expressive of profound toxemia and warrants a poor prognosis.

Fatal peritonitis occurred in 3 cases and obviously rates in the same category as meningitis as a complication which foretells a fatal termination

The other complications tabulated were so rarely observed that discussion is of little consequence

TREATMENT

The problem of evaluating treatment was attacked with some trepidation. Lobar pneumonia, like many other diseases, has run the gamut of therapy, but the consensus of modern authorities resolves the treatment into oxygen and specific serum when indicated. In this series an attempt has been made to draw some conclusions from the various drugs and therapeutic measures used in the past nine years (figure 12)

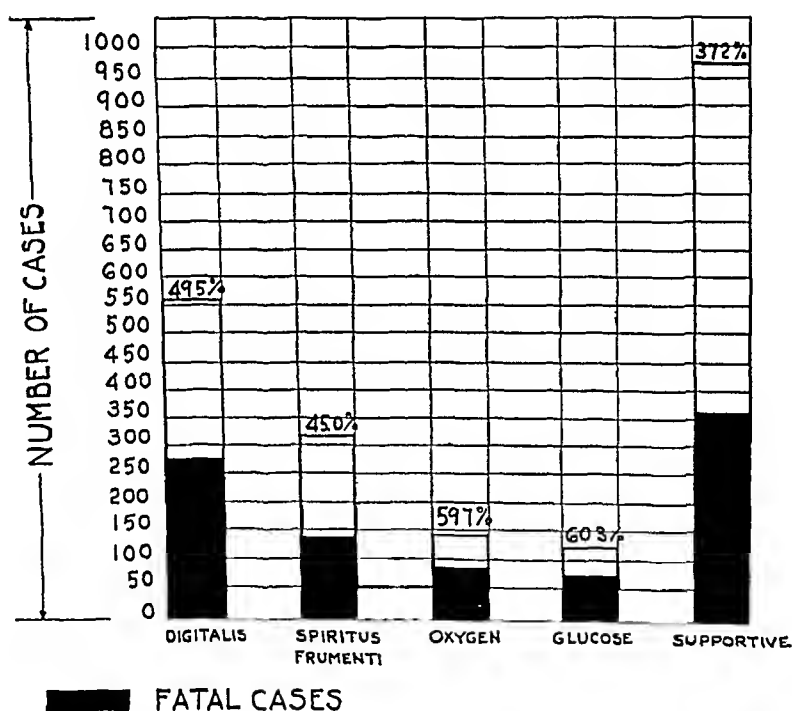


FIG 12 Therapy of lobar pneumonia with mortality

The first drug considered was digitalis. This was used in 557 patients with a mortality of approximately 50 per cent. The majority of those who received digitalis entered the hospital during the years 1927 to 1930. All were digitalized routinely. During the past few years, Cohn and Lewis,¹⁷ working at the Rockefeller Institute, have shown that the mortality is actually higher in the digitalis-treated groups. Inasmuch as the mortality in our patients treated with digitalis was nearly 50 per cent, this conclusion seems to be well-founded. Since 1930, digitalis has been used in pneumonia

cases only when such indications as grave cardiac irregularities, auricular fibrillation or congestive failure developed.

The second type of therapy investigated was the use of alcohol in the form of whiskey. This drug was largely used by our medical forefathers and is still used routinely by many physicians today. In 320 patients treated with routine doses of whiskey the mortality was 45 per cent, or 7 per cent higher than the general mortality. This drug, like digitals, has also been discontinued during the past few years and is now reserved specifically for the chronic alcoholic who, in the face of pneumonia, may develop delirium tremens if it is omitted.

Oxygen, the third most commonly employed therapeutic measure, was administered to 149 patients with a mortality of approximately 60 per cent. To the casual observer, this high mortality might be interpreted as minimizing the value of this form of therapy. Some explanation is obviously necessary. Most of the patients who received oxygen were cases showing marked cyanosis, dyspnea or grave circulatory failure. In other words, the majority of these cases probably would have ended fatally whether or not oxygen were used. It should also be stated that the majority of these patients received oxygen by means of the mask, which is now known to be the least effective method of administration. The cases treated in this fashion obviously occurred in the days prior to the use of nasal catheter or the development of oxygen tents and oxygen chambers. Only a few of the patients were given oxygen early in the course of their disease. There is no doubt in our minds that early oxygen therapy, given by the proper methods, is a valuable therapeutic agent.

Glucose (20 per cent dextrose) was given intravenously to 121 patients, and was followed by a 60 per cent mortality. The same applies to glucose as applied to oxygen, namely, that this drug was also used in cases of evident circulatory failure where an unfavorable outcome was anticipated. Even with this high mortality, we believe that the use of this drug intravenously often turns the tide in a favorable direction.

The last form of therapy investigated has been listed under the general term of "supportive treatment." By this term is meant the use of any drug, which can be employed to support the patient in a general way. The judicious use of morphine, codeine, caffeine sodium benzoate, salicylates and quinine may be considered under this heading. The latter drug was used in about 90 per cent of the patients treated by so-called "supportive measures." It has a long reputable record in pneumonia therapy. During the past decade, a closely related drug, optochin, has been highly regarded as a pneumococcicidal agent. Inasmuch as no one has proved any deleterious effect, and, as there may be some beneficial result from quinine administration, it has been retained as a routine therapeutic measure. It should also be mentioned that the combating of toxemia through establishing improved water balance by means of forced fluids orally, and saline administered parenterally is also a valuable and important factor included under the term

“supportive measures” Likewise good nursing care must be included under this blanket term The patients treated merely by “supportive” treatment had the lowest mortality, 37.2 per cent

Pneumothorax was used in seven selected cases with only one death This number is too small to draw any conclusions therefrom

Specific type I serum was also used in such a small number of cases that any clinical deductions are unwarranted

SUMMARY AND CONCLUSIONS

An analysis has been made of the records of 1298 patients having lobar pneumonia observed at the Buffalo City Hospital from 1927 to 1935, inclusive

The mortality rate for the entire series was 38.5 per cent

The incidence of lobar pneumonia and the mortality rate varied considerably from year to year

The incidence of lobar pneumonia varied materially from month to month but regardless of whether it occurred in the winter or summer, the mortality was approximately the same

The mortality rate was highest at the extremes of life and lowest between the ages of five and ten From ten years to old age, the mortality was directly proportional to the age

Lobar pneumonia was three times as common in men as in women and the mortality rate was approximately 10 per cent higher

The mortality rate among northern negroes was less than in the white race

The mortality rate in chronic alcoholics was approximately twice that of non-alcoholic patients

The presence of syphilis materially increased the mortality rate, although no relationship was demonstrated between syphilis and delayed resolution

Chill was not as common a symptom as has previously been believed

Lobar pneumonia, involving one or more lobes of the right lung, was one and one-half times as frequent as left-sided involvement Multi-lobar involvement and bilateral involvement add considerably to the mortality rate and the gravity of the prognosis

Leukopenia, and leukocytoses above 50,000 were serious prognostic findings

Type IV pneumonia was the most commonly observed type, while type III was accompanied by the greatest mortality The greatest number of complications was observed in type I, while the least was seen in type III Type III was the most commonly observed type in patients over 40, type I being the preponderant type in adolescence and early life

Empyema, pleural effusion, and otitis media were the most frequent complications in the whole series, while pericarditis, meningitis and peritonitis were the most fatal

The effect of routine therapeutic measures upon the mortality rate was inconclusive

The authors wish to express their appreciation to Dr Carroll J Roberts for his valuable suggestions and criticisms, and to Drs V Boeck, D Levy, and A Cirrincione for their assistance in the compilation of the statistics

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FURTHER OBSERVATIONS OF THE HISTIDINE TREATMENT OF PEPTIC ULCER

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IN 1923, Mann and Williamson¹ reported that they were able to produce in dogs subacute and chronic peptic ulcers, quite like those found in man, by diverting to another part of the intestine those secretions of the duodenum which normally neutralize the gastric juice as it leaves the stomach

Aron and Weiss² of Strasbourg repeated and confirmed these studies. They came to the conclusion that these ulcers formed as a result of an amino acid deficiency. On this theory, they gave intramuscular injections of certain amino acids to dogs that had been subjected to the Mann-Williamson technic, and found that daily injections of 5 c c of a solution of 4 per cent histidine and 2 per cent tryptophan would prevent the development of ulcers in the dog. This experimental work was followed by clinical trial in ulcer patients with marked success, according to their report.

In the due course of time following the publication of Aron and Weiss, other encouraging communications on the use of histidine in the treatment of peptic ulcer began to appear in the foreign literature and eventually, largely through the extensive advertising claims of one of our pharmaceutical companies, the physicians of this country were informed of this work and the results reported by European investigators.

The treatment of peptic ulcer constitutes such a major therapeutic problem that any plausible aid that holds the possibility of a cure or the elimination of the usually accepted, protracted routine of bed rest, milk, alkali powders and diet over a period of months, seems to us to be worthy of consideration, so, with this thought in mind, we began to treat a series of peptic ulcer patients with a series of 24 daily intramuscular injections of 5 c c of 4 per cent histidine monohydrochloride †.

Since January 1935, we have treated 42 roentgen-ray proved cases of peptic ulcer. Of these 42 cases, we have been able to carefully follow and recheck closely the clinical and radiographic progress of 28 cases, all of which have been observed for at least one year following the treatment. Due to the natural vagaries of ulcer symptoms, we called attention in an earlier preliminary report³ to the necessity of conservative conclusions on immediate results. However, in view of the fact that most remissions in ulcer patients will not last for as long as a year, we feel that although our series is small, we can at this time draw fairly accurate deductions as to the value of the treatment, both from the standpoint of immediate and final results.

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† Larostidin—Hoffman-LaRoche, Inc.

In order that the conclusions from this study might be judged entirely on the effect of this treatment alone, these patients were requested to carry on their usual activities of life, were given no medicine whatsoever, and advised to eat a general diet. This latter suggestion was somewhat difficult to carry out inasmuch as most of these patients had already taken one or more medical cures and were aware of the efficacy of frequent feedings and alkalies. The patients who obtained relief with the first few injections were quick to branch out on their diet, but the more resistant cases were reluctant to take on foods that they felt had formerly caused trouble.

These cases were in no way selected but routinely placed on the treatment when they presented themselves to the clinic, regardless of the nature of their ulcer. By this method of choice, it is obvious that some cases of perforating and stenosing ulcers which could not normally be expected to respond to medical therapy were included in the series, so, we have shown in the following charts not only the results obtained in the entire series, but also the results obtained in 21 selected cases. The latter group was composed of such cases as showed uncomplicated peptic ulcer and no other physical ailment.

The group is composed of 17 males and 11 females, whose ages varied from 20 to 72 years, the average being 45.2 years (table 1)

TABLE I
Age and Sex

Age	20-29	30-40	41-50	51-60	61-70	71-80
Male	2	5	4	2	3	1
Female	2	3	3	3	—	—
Average age	45.2 yrs		Total cases		28	
Total males	17		Total females		11	

A history of typical ulcer symptoms, with intermittency, food and alkali relief, and epigastric distress two to four hours after meals, was presented in about 90 per cent of the cases (table 2). Four of the patients had had previous hemorrhages. Two cases gave a history of perforation and three cases presented an entirely atypical symptomatology, the diagnosis being

TABLE II
Symptomatology

Epigastric pain or distress	25 cases
Intermittency	26 cases
History of food and alkali relief	24 cases
Hemorrhage	4 cases
Perforation	2 cases
Atypical symptomatology	3 cases
No food or alkali relief	4 cases
Avg. duration of symptoms	8.8 years

established entirely by roentgen-ray findings. The average duration of symptoms was 8.8 years.

Of the 28 cases in the series, 23 were duodenal and five were gastric ulcers (table 3). The roentgen-ray findings were rechecked every three months for one year and at the end of this time two cases of the duodenal

TABLE III
Radiographic Results

<i>Duodenal</i>	
Cured	2 cases
Improved	5 cases
Unimproved	16 cases
<i>Gastric</i>	
Cured	0 cases
Improved	0 cases
Unimproved	5 cases

ulcer group were considered cured. This deduction was based on the disappearance of all deformity of the cap, as well as a clinical course in which there had been no recurrence of symptoms. Decreasing size of the crater, improvement in the appearance of the bulb, and decreasing activity of the stomach were the criteria on which five cases in the duodenal group were considered improved radiographically. Sixteen of the duodenal cases were unimproved from the roentgenologic viewpoint. None of the five cases of gastric ulcer showed any improvement radiographically. Analyzing these figures, we find that approximately 75 per cent of the cases showed no improvement radiographically, while 86 per cent were considered cured and 21.7 per cent improved.

The clinical results of the entire series show six cases or 21.4 per cent received complete and total relief (table 4), a figure considerably higher than the percentage considered cured radiographically, but a percentage quite in keeping with the radiographic findings if we consider the number of cases

TABLE IV
Clinical Results in Entire Series

Duration of Symptoms	No. of Cases	Complete Relief	Partial or no Relief	Complete Relief with Relapse
1-3 yrs	7	3	2	2
4-5 yrs	3	0	2	1
6-10 yrs	10	3	3	4
11-14 yrs	3	0	2	1
15-20 yrs	3	0	1	2
21 plus	2	0	1	1
Total cases	28			

cured and improved radiographically. This discrepancy is possibly due to the fact that some cases cured clinically may not have been considered cured radiographically because of a remaining scar in the duodenal cap. Eleven cases, or 39.3 per cent, received only partial or no relief, and 11 cases, or 39.3 per cent, received complete relief but relapsed within the first year following treatment. Adding the percentages of the relapsing group to those that received only partial or no relief, we find approximately 80 per cent of the patients received no real permanent benefit from the treatment. However, if we group the relapsing cases that received complete relief with those that received permanent relief, we find that 60 per cent of the patients obtained symptomatic relief, a percentage somewhat lower than our experience with the Sippy management of peptic ulcer.

In the group of 21 selected cases, we find 28.6 per cent of the cases received permanent relief, 23.8 per cent were complete failures, and 47.6 per cent received complete, immediate relief with relapse within the first year (table 5). This group of cases probably more nearly represents the true curve of success and failure, as the stenosing and perforating cases were not included in the final deductions.

TABLE V
Clinical Results in Uncomplicated Cases

Duration of Symptoms	No of Cases	Complete Relief	Partial or no Relief	Complete Relief with Relapse
1-3 yrs	7	3	2	2
4-5 yrs	2	0	1	1
6-10 yrs	7	3	1	3
11-14 yrs	2	0	1	1
15-20 yrs	2	0	0	2
21 plus	1	0	0	1
Total cases	21			

Ten of the patients from the selected group were given a second course of treatment four to six months after finishing the first course, regardless of whether or not they had relapsed within that period. It is interesting to note that of this group, those patients who had previously relapsed have all developed symptoms again following the second course of treatment.

One uncomplicated case has received four courses and has relapsed within 30 to 60 days following each course, although he received complete relief from symptoms during each period of treatment. Sandweiss⁴ has reported that several of his cases became symptom-free with a daily intra-muscular injection of water. We are of the opinion that possibly the above case would be an excellent subject on whom to determine the psychological effect of injection treatment.

Two uncomplicated cases have received three courses of treatment, and all have relapsed from three to seven months after the treatment. The case that relapsed seven months after the treatment shows the longest period of freedom from symptoms that we have found in the relapsing group.

Two of our cases have been operated upon four to six months respectively after the completion of the injections, and in both instances active ulcers were present. One other case died of intra-abdominal complications four months after completing the treatment, and an active duodenal ulcer was found at the necropsy.

In our earlier report, we were of the opinion that the cases in which symptoms had not been present longer than five years were the ones most likely to be benefited, but in the final analysis, we find three cases cured who had had symptoms from six to 10 years, and three cases whose symptoms were less than five years in duration. So it is apparent that the duration of the ulcer has made no difference in the final results except from the standpoint that none of the remaining cases with symptoms for more than 10 years received any improvement.

It has been our experience that most of the patients who received complete relief became symptom-free with the first few treatments, and those cases who received no early benefit did not improve with increasing the number of treatments, as we gave several patients 30 daily injections. One case received 38 daily treatments with no improvement whatever, but became symptom-free on a carefully managed Sippy routine. We have experienced no reactions in any of the 42 cases we have treated and are of the opinion that the treatment is perfectly harmless.

In conclusion, we would like to call attention again to the fact that this treatment will undoubtedly produce remissions in a fairly high percentage of uncomplicated ulcer patients, 76.2 per cent in the selected series, but the permanent relief is no greater than that in various other methods of ulcer treatment and management. We have purposely not used the histidine treatment in conjunction with dietary and alkali routine because we felt that if the treatment were worth while, one of the greatest advantages it offered was the possibility of eliminating the monotonous routine of our usually accepted measures. We also felt that if peptic ulcers were due to histidine deficiency, as proposed on theoretical grounds by the originators, dietary measures would not be necessary. We were able to produce a remission with histidine in only one case of the four in whom dietary and alkali regime had previously failed to give relief. After two years' experience in the treatment of 42 patients with histidine, we are of the opinion that the results obtained do not justify the routine use of this procedure in the management of peptic ulcer patients.

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STUDY OF HYPERTENSION IN VETERANS¹

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IN the period from October 1, 1935 to April 1, 1936, the Veterans' Administration Facility in Washington, D. C., discharged 1369 patients who had been under observation and treatment in the wards. Of this number, 82 had hypertension, which is approximately 6 per cent of the total number discharged. Riseman and Weiss¹ quote reports from two European hospitals in which the incidence of hypertension among the male patients examined was 9.6 per cent and 9.7 per cent respectively, and among the female patients 7.9 per cent and 25.9 per cent of the total number of women. In these reports, however, a blood pressure above 140 mm Hg systolic was considered abnormal, while in this series, the figures of 150 mm Hg systolic and 90 mm Hg diastolic have been used as the dividing line. The diagnosis of hypertension depends to some extent upon the examiner, the conditions under which the examination is made, and the reactions of the patients, thus, a single estimation of pressure may be too high, particularly if the patient is under emotional stress. Alvarez² reported hypertension in 53.6 per cent of drafted men, which suggests that the emotional tension of an examination under such conditions increased the blood pressure of a considerable number of healthy men.

The present group under study is composed of veterans of the military services of the United States who were patients in this hospital. Many of them were observation cases and had not previously known of their hypertension.

Only 4.7 per cent of the whole discharged group were females of whom six comprised 7.3 per cent of the hypertensive group.

Among the men, the colored patients represented 8.2 per cent of all discharged and 20.7 per cent of the hypertensive cases. This disproportion is sufficiently great to indicate a greater incidence of hypertension in negro men than in white patients from the service groups.

A characteristic of the population in Veterans' facilities is the limited age period into which the majority of the patients fall. While the range for approximately 1600 patients was from 23 years to 92 years, the average was 45 years with 58.5 per cent between 40 years and 49 years. The average age of all the hypertensives was 49.8 years or approximately five years older than the whole group, with 51 per cent between 40 and 49 years. The colored patients with hypertension averaged 45.5 years of age, while the females with hypertension averaged 52.3 years. The latter group is too small to influence the figures greatly or to be more than suggestive of the trend, but it is significant that the Negroes not only have a relatively higher

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incidence of hypertension but the average age at which they appear for treatment is less than that of the white patients (table 1)

TABLE I
Incidence of Hypertension

Age	Controls		Hypertensives	
	Number	Per cent	Number	Per cent
20-29	6	0.3	1	1.2
30-39	374	23.3	11	13.4
40-49	937	58.5	42	51.2
50-59	188	11.7	10	12.2
60-69	73	4.6	12	14.6
Over 70	24	1.5	6	7.3

WAR SERVICE AND POST WAR OCCUPATION

Sixty-four patients in this group were in the Service during the World War, one was a veteran of the Civil War, 11 were Spanish-American War veterans, and the remainder were in peace-time service. Among the World War veterans, 32 were overseas, and some engaged in varying amounts of combat service. The records show that six of these received gunshot wounds which in themselves were not severe enough to cause permanent disability, 10 claimed to have been gassed, in most cases with mustard gas, and a total of 26 gave histories of illness or injuries at home or abroad during their service, that may have affected their health subsequently. It is inferred that these men were physically fit upon entering the Service and were more or less disabled following their war-time experiences, although there is no common factor unless it be emotional strain that might account for the development of hypertension.

In many instances, high blood pressure and its complications have not been the reason for seeking medical care. Five patients have been unable to do any work or very little work since discharge from Service. One was discharged because of an injury to his back with subsequent hysterical manifestations, one had a gunshot wound followed by empyema, one had measles with severe complications, one was apparently well on discharge but developed symptoms and signs of serious cardiac disease within two months after discharge, one has been only partially active following pneumonia, and one has worked very little since the Service but did not have a medical record during his enlistment. Another veteran worked intermittently until 1928 but had some degree of heart failure since 1918.

With the exception of the traumatic disabilities, the illnesses most frequently noted were influenza, pneumonia, and rheumatism of various types. The Spanish War veterans usually gave a history of having had malaria, and one man who developed malaria in 1919 stated that he had not been well since. One veteran, who was in the Navy, made over 225 deep-sea dives up to 170 feet and was always sick after coming to the surface as he was

not decompressed. He has an excessively high pressure which has disabled him since the age of 32. It is impossible to say how important these illnesses and traumatisms were in causing hypertension, but in 19 of the 26 cases with wartime medical records, the hypertension was first noted before the age of 40, the average age of diagnosis being about 38 years for these 26, as compared to 41 years for the whole hypertensive group of World War veterans. The earlier recognition of hypertension in those patients who had wartime illness or injury may be due to more or less continuous observation since their discharge.

Official records of 11 patients were available for diagnoses and treatment rendered before the appearance of clinical hypertension was noted.

One patient was first seen in 1931, at which time he gave a history of life-long headaches. He had taken large quantities of a proprietary analgesic. He was an aviator during the War, had influenza and malaria in 1918 and 1919, since which time he had never felt well. In 1931, his blood pressure was 136 systolic and 86 diastolic, his retinal arteries showed moderate sclerosis, the blood chemistry and urine were normal. In 1933, the blood pressure was recorded between 174 and 200 systolic and 106 and 128 diastolic. In 1935, he died of an intracranial hemorrhage following congestive failure.

The headaches and cerebrovascular changes as shown by sclerosis of retinal arteries preceding the hypertension, suggests a relationship between the intracranial circulatory changes and the hypertension.

The second case was seen in 1931 because of gastrointestinal complaints. His blood pressure during that admission was 138 systolic and 80 diastolic, and definite retinal sclerosis with bilateral neuroretinitis was observed without evidence of renal or cardiac damage. In 1933, he was given a diagnosis of hypertension, and in 1935, the blood pressure was 170 systolic and 110 diastolic. He was admitted for treatment of cardiac failure and showed generalized arteriosclerosis, cardiac enlargement, bundle branch block, normal blood chemistry except for a uric acid of 4.8 mg per cent, a trace of albumin and occasional hyaline cast in the urine, and normal P S P (phenolsulphonephthalein elimination). This patient was 39 years of age when first observed. His father had died at the age of 31 of "acute indigestion."

In this case again, the changes in the retinal arteries were the first evidence of vascular disease noted and this suggests that the intracranial vascular lesions preceding the clinical hypertension may have been important causally, although generalized vascular sclerosis appeared comparatively early.

The third patient had been seen in various facilities and offices since 1922. During the War, he had had measles followed by otitis media and arthritis which persisted and greatly crippled the patient. In 1926, he was diagnosed dementia precox and possible endocrinopathy. In 1927, an albuminuria was noted, in 1931, an iritis resulting in loss of vision in one eye and partial loss in the other, and in 1932, hypertension. In 1936, his blood pressure was 170 systolic and 110 diastolic, the blood chemistry was normal except for a blood uric acid of 4.2 mg per cent, and no other evidence of renal disease was found. There was slight cardiac enlargement. The patient still complained of his arthritis, and his mental condition had required institutional care on several occasions.

The severe chronic arthritis and otitis media, the mental illness, and the possible endocrine dysfunction were the important conditions preceding the development of hypertension in this patient.

The fourth patient had been treated in Veterans' Administration facilities since 1923. He had otitis media while in the Service which continued as a chronic sup-

puiative otitis media until 1926 when a mastoidectomy was done. This was followed by a thrombosis of the lateral sinus and an extradural abscess in the middle fossa. He had had headaches since the War and in 1931, a retinitis suggestive of hypertension was noted. At this admission, his blood pressure was 120 systolic and 70 diastolic but his urine showed some albumin, casts, and red blood cells. The blood chemistry and P S P were normal. In 1936, the blood pressure was 144 systolic and 96 diastolic, the blood chemistry and P S P were still normal except that the blood uric acid was 4.9 mg per cent, and the urine showed a trace of albumin and an occasional hyaline cast.

The history of an ear infection persisting for almost 10 years, resulting in an extradural abscess and the evidence of renal involvement with retinal changes may be important.

The fifth patient had been seen in Veterans' Administration facilities since 1919. He had had various diagnoses of hysteria, petit mal, epilepsy and constitutional psychopathic state. During the War, he had rheumatic fever but later saw active service and received a gunshot wound. He was hospitalized on several occasions in mental institutions for psychotic episodes. In 1931, he was observed to have a low grade retinitis with small arteries which showed thickening. The blood pressure at that time was 110 systolic, 90 diastolic, and the urine was negative. In 1934, the blood pressure was 178 systolic, 126 diastolic, the blood chemistry and urine were normal except for a uric acid of 4.9 mg per cent.

This patient was 37 years of age when hypertension was first discovered and changes in the retinal arteries had been noted three years before. He also had mental illness with psychotic episodes.

The sixth patient, a colored veteran, had been seen from 1922 in Veterans' Administration facilities. He had pneumonia during his service and never returned to duty following his illness. Since 1922, he had been diagnosed pulmonary tuberculosis by some and no pulmonary disease by others. Hypertension was first noted in 1929 when the patient was 36 years of age. In 1936, his pressure was 196 to 220 systolic and 130 to 136 diastolic.

The patient had been very nervous, restless and easily frightened, but no definite cause for his disability prior to the hypertension was found except the sequelae of the pneumonic infection.

The seventh patient had been under treatment since 1919. During the War, he was gassed and claimed to have been shell-shocked, following which he was very nervous with many complaints suggesting neurocirculatory asthenia. He was diagnosed chronic bronchitis, tuberculosis by some and not by others, psychoneurosis by some and not by others. In 1934, he was given a diagnosis of hypertension and nephritis. In 1935, his blood pressure was 176 systolic, 116 diastolic, the blood chemistry was normal except for a uric acid of 4.2 mg per cent. The urine showed 4-plus albumin, hyaline and granular casts. The P S P was normal.

The diagnosis of nephritis apparently was based on the presence of hypertension and abnormal urinary sediment, without any history of an acute attack. It was felt, at a later date, that this patient did not have a nephritis primarily but showed renal dysfunction secondarily to hypertension. The trauma during the War and the succeeding psychoneurosis are outstanding in the history preceding the diagnosis of hypertension.

The eighth patient had been seen from 1921 in Veterans' Administration facilities. During the War, he was hospitalized with rheumatism of his legs and erythema nodosum. This condition recurred in 1920 and 1933, as well as an otitis media in 1930. He had had diagnoses at various times of diseased tonsils, effort syndrome, and hypertension in 1931 for the first time. In 1935, his pressure was 156 systolic and 108 diastolic. The blood chemistry was normal except for a uric acid of 4.2 mg

per cent, and the urine was negative. The basal metabolic rate was minus 15 per cent, and he weighed over 200 pounds.

The diagnosis of hypertension was made at the age of 32 years. He had a history of rheumatic infection without cardiac involvement. The comparatively mild hypertension may have been associated with an endocrine dysfunction suggested by the obesity and low basal metabolic rate.

The ninth patient had been seen since 1922 in Veterans' Administration facilities. He was qualified for limited service during the War because of a previous fracture of the left tibia. Since 1918, he had had arthritis requiring bed care for several months of every year. In 1929, a diagnosis of uncomplicated nephritis was made which improved with treatment. In 1934, hypertension was first noted on his record, and in 1936, his blood pressure was 205 systolic, 120 diastolic. There was retinal and peripheral arteriosclerosis. The blood chemistry was normal except for a uric acid of 5.4 mg per cent, and the P S P was normal. The urine showed a trace of albumin in several specimens and an occasional hyaline cast which was not considered sufficient to make a diagnosis of nephritis.

The recurring chronic arthritis with a fairly high uric acid may indicate that the patient had gout since the other renal findings are no greater than might be expected with a blood pressure of over 200 systolic. This patient was a painter by occupation but gave no history of lead poisoning and he had not worked since 1932.

The tenth case had been seen in Veterans' Administration facilities since 1928 and given diagnoses ranging from psychoneurosis with depression to toxic psychosis. When first observed in the hospital in 1930, his blood pressure was reported as 130 to 142 systolic and 90 to 106 diastolic. He stated that since boyhood he had been "high-strung," resented authority, and wanted to be free and independent. He claims to have been slightly gassed and knocked unconscious by an exploding shell during service and at the time of discharge was very nervous. The diagnosis of psychoneurosis, moderately severe, has been continued up to the present.

This patient presents a tense mental reaction without other evidence of organic illness as a possible explanation of his hypertension.

The eleventh patient, a dentist, had been seen as a patient in Veterans' Administration facilities since 1924. In November 1924, he was examined for a Reserve Commission, at which time the blood pressure was reported as 130 systolic and 87 diastolic, heart and arteries normal. Later in the same year, he was given a diagnosis of mitral stenosis which was repeated on several occasions subsequently, as well as the diagnosis of neurasthenia, but in 1936 there was no evidence of heart disease. Hypertension was first noted in 1929. The patient dates his symptoms to the bombing of the hospital in which he was on duty in France, and injury to his head when thrown by the force of the explosion. Since then, he claims that he has been a changed person and has not been able to practice because of his nervous tremor and tension.

There is very little in this patient's history except the long-standing neurasthenia and possible cranial trauma to account for his hypertension. The neuropsychiatric consultant made a diagnosis of cerebral arteriosclerosis apparently on the basis of his mental reactions.

In this group which had been under observation for 5 to 17 years prior to the last admission to the hospital, the medical histories are very dissimilar. Four had had arthritis of various types, three had had otitis media, one with mastoiditis and extradural abscess, one had had pneumonia, one influenza, and one malaria. There were no histories of acute nephritis in this series. The histories of infections during Service are not much different from what might be expected in a civilian population, and the cases are too few to

demonstrate any relation between specific infections and hypertension. Only one patient in this series developed tuberculosis during the War and this one was a female whose hypertension appeared many years after her pulmonary condition was quiescent. Several others were suspected of having tuberculosis but the later course would indicate that this was not the case.

Syphilis has frequently been cited as a causative factor in essential hypertension although this is denied by most authors in recent years. Among the patients who had hypertension, eight had positive blood Wassermann reactions, one a positive Kahn reaction and negative Wassermann and six gave definite histories of syphilitic infection although their blood Wassermann reaction was negative while in the hospital. Fifteen patients, all of whom were males, is an incidence of approximately 18 per cent. A diagnosis of syphilis on the basis of a positive Wassermann reaction only was made on 64 of the whole discharged group or approximately 5 per cent. The incidence of syphilis among the hypertensives is greater even if only Wassermann positive cases are considered, but it is perhaps most important that 11 of the 15 patients or 73 per cent were colored, which is 65 per cent of the total number of colored patients with hypertension. Among the white patients with hypertension, the occurrence of syphilis does not vary significantly from the general incidence. In the Negroes, syphilitic infection if not the basic cause of hypertension, may account for the early development and the severe forms with frequent vascular accidents.

In four of the preceding patients, examination of the retina revealed sclerosis of the vessels several years before hypertension was noted clinically. It has been postulated before that vascular lesions in the brain³ are responsible for many instances of hypertension although Cutler⁴ has offered considerable negative evidence to the contrary. The presence of cerebral arteriosclerosis as indicated by changes in the retinal arteries, before the development of any definite elevation of blood pressure, however, would further suggest the importance of cerebral vascular changes in the causation of essential hypertension.

At least four patients gave histories of cerebral trauma from falls or explosions in their immediate vicinity. One also had done considerable deep-sea diving without decompression which is said to frequently cause intracranial vascular changes. The possibility that cranial trauma may cause brain lesions, resulting in chronic hypertension in some cases, is suggested. It is unlikely that this could be proved by histological studies in view of the limited knowledge of central control of vasomotor centers and the anatomical pathways involved.⁵

NEUROPSYCHIATRIC CONDITIONS

In the group under study who exhibited hypertension, 11 patients were given diagnoses of organic and functional mental disease of various kinds. Five were classified as having dementia praecox, one paresis, one senile

psychosis and four severe psychoneurosis. Several others complained of psychoneurotic symptoms of more or less severity, but the above four developed their illness during the War. The influence of chronic anxiety states and other mental illness on the development of chronic hypertension can only be surmised, but it is true that these conditions are present in many cases before the blood pressure becomes chronically elevated. The effect of emotion in raising the blood pressure acutely is commonly observed and the "high pressure," "quick-tempered," individual not infrequently has hypertension.

As an indication of psychoneurosis, it is interesting that at least eight of the hypertensive patients were addicted to the use of alcohol in large quantities. Thirty-one admitted the moderate use of alcohol and 24 did not use it.

OBESITY

In the series of 82 patients with hypertension, 24 gave a history of obesity in the past or at the time of their admission. These patients had at some time weighed over 200 pounds, which for most individuals is definitely above normal. The age, weight and sex were not considered in this classification but a comparison was made with the incidence of individuals weighing 200 pounds or over, at some time in their life, in a group of 80 patients who had diagnoses of benign tumor, cardiac neurosis and urticaria. None of this latter group suffered from hypertension or wasting illness and only four weighed over 200 pounds. The frequent occurrence of hypertension among obese individuals has often been observed although the mechanism or significance of the relationship cannot be explained.

Endocrine disturbance is often present in both conditions and one of our patients presented a fairly typical picture of a Cushing syndrome with obesity, hypertension and diabetes. Three other patients had diabetes, two of whom were obese while the third was not. The latter patient was 71 years of age and had a comparatively mild diabetes. Hypertension has been reported occurring frequently in diabetes but diabetes is present in only a small percentage of hypertension patients ^{6, 7}

HEREDITY

Information regarding the illnesses of other members of a family is rarely sufficiently complete or accurate to draw definite conclusions concerning the hereditary influence involved in any particular type of illness, the colored patients, especially, often know very little about their parents or their brothers and sisters. Fourteen records did not contain any statement regarding either parent. However, of these patients, 10 were over 60 years of age themselves. The age of the parents at death was shown for 48 fathers and 47 mothers, the average being 65 years and 60 years respectively. The fathers of seven patients were still living and their average age was 73.

years, while 13 mothers were still living with an average age of 69 years. In a few other instances, the ages of the parents were not known, but it is likely they would only have raised the average age as the statements were made that they died of old age or were old and feeble. These figures would indicate that the males survived the females by several years and that the longevity of the parents of these patients with hypertension was well up in the normal range of life expectancy. Practically all of the deaths of parents in earlier life were due to acute infections, accidents and child-bearing, and only four deaths before the age of 60 were from heart disease.

At least 37 of the veterans had one member of their family, composed of their parents and siblings, who had died or were suffering at that time from some form of cardiorenal-vascular disease, the most common being a cerebral accident. Fourteen of these were in brothers and sisters below the age of 60. Eleven families had two members, and four families three or more members beside the veteran patient, with cardiovascular-renal disease.

Compared to a group of 80 non-hypertensive patients, the proportion of parents whose age at death was known in both groups was about the same and the average age at death was several years greater in the parents of the hypertensive patients. The age of a few more of the living parents of non-hypertensive veterans was given than in the other group, but here again, the average age is somewhat greater in the parents of hypertensive patients (table 2).

TABLE II
Parents of Veterans

	No Patients	Fathers				Mothers			
		Dead	Av Age Death	Living	Av Age	Dead	Av Age Death	Living	Av Age
Hypertension	82	48	65	7	73	47	60	13	69
Non-Hypertension Control	80	46	62.8	16	70	41	55.4	16	66

There is a definitely greater incidence of cardiovascular-renal disease in the immediate families of hypertensives than in the non-hypertensive group as indicated by the table (table 3). It is suggestive also that 22 members of the families of the hypertensive patients had had strokes, apoplexy or

TABLE III
Number of Families with Cardiovascular Disease in Other Members than Patient

	Hypertension	Non-Hypertension Control
One other member	37	21
Two other members	11	4
Three or more other members	4	1

paralysis while only three relatives of the non-hypertensive patients had had such conditions as indicated by the records

Twenty-one patients were given a diagnosis of hypertension before the age of 40 and of these, there was at least one other member of the family with cardiovascular-renal disease in nine. This is about the same proportion as in the whole group

The family history of the patients that died showed a high incidence of cardiovascular-renal disease in six, and the other two did not give adequate histories

It is reasonable to suppose that constitutional factors, familial reaction patterns, and habits of living are of some moment in the development of hypertension. This study is suggestive of this influence as indicated by the greater incidence of cardiovascular-renal diseases in the families of patients with hypertension as compared to a non-hypertensive group although the longevity of the parents favored the former. Even those parents who died of cardiovascular-renal disease were on the average above 60 years of age, and not infrequently the statement was made that the parents were over 70 or 80 when they died of a stroke

OCCUPATION

The occupation record was given quite completely in all cases except 10 which included those veterans who had not worked since discharge from service and those who had retired many years previously because of age or disability. Five groups were separated on the basis of the physical work involved in their occupation: 1, clerical work, 2, salesmen and shopkeepers, 3, professional people including doctors, dentists, lawyers, nurses, and army officers, 4, heavy laborers such as farmers, blacksmiths, machinists, laborers, etc., 5, light laborers such as carpenters, painters, housewives, chauffeurs, etc. It obviously is impossible to accurately classify physical effort so dogmatically, but the following distribution with the average age is presented and attention is directed to the low average age of the salesman group and the comparatively higher average age of the clerical and professional groups as compared to the laboring groups. The rather high percentage of the professional class in this series from a general service hospital suggests a high frequency of hypertension in individuals in such occupations (table 4)

TABLE IV
Occupation and Hypertension

	Class	No. Patients	Per cent	Av. Age at Obs.
Clerical	1	10	12.2	52.1
Salesmen, etc	2	12	14.6	44.4
Professional	3	13	15.8	54.7
Heavy laborers	4	18	21.9	49.6
Light laborers	5	19	23.1	46.7
Unclassified	6	10	12.2	56.9

It is impossible to say from the records whether the individuals in the salesman group were high pressure types or not. It seems more likely that they were men with some physical handicap for which they sought treatment earlier and who chose an occupation permitting some irregularity of attendance.

As would be expected from such a hospital population, the laboring groups are the largest. Speculation as to the significance of the younger average age is covered in the next section.

CARDIAC ENLARGEMENT

In many instances, the 82 patients exhibiting hypertension were admitted to the hospital primarily for treatment or study of other conditions. Thirty-four were found to have no objective evidence of heart disease and in six patients with hypertension, the cardiac involvement was considered to be principally of syphilitic etiology.

The average age of the hypertensive patients without heart disease was 49.5 years, only slightly less than the general average for the whole group. Thirty-nine patients were considered to have cardiac enlargement and their average age was 51.5 years. As far as could be determined from the histories given by the patients and the previous records, the patients with cardiac enlargement had been diagnosed hypertensive an average of four years before their present admission, while in the whole group, the presence of hypertension had been known on an average of nine years.

When the incidence of enlargement in the various occupational groups was compared with their proportion of the whole group, it was observed that the heavy laboring group was responsible for the largest percentage with cardiac enlargement, definitely greater than the per cent of this class in the whole group. The salesman and shopkeeper group also showed a higher percentage with cardiac enlargement than would be expected from their representation in the group. Excessive exertion might be expected to contribute to cardiac enlargement but such an explanation is hardly applicable to the salesman group which also showed a low age at the time of observation.

Twenty-six per cent of the patients with enlarged hearts were colored while approximately 21 per cent of the hypertensive group were colored, indicating not only a high incidence of hypertension but also a high per cent with cardiac involvement. The facts that the colored veterans were largely engaged in laboring occupations and that 65 per cent of them had syphilis are undoubtedly important for the explanation of this racial tendency to cardiac involvement.

All the patients with mean pressures above 170 mm Hg had cardiac enlargement. Most of the patients with comparatively low mean pressures also showed cardiac enlargement but their histories and electrocardiograms indicated previous attacks of coronary occlusion or hemiplegia.

Thirty-eight per cent of the patients with enlargement also weighed or had weighed over 200 pounds. Thus 60 per cent of the obese patients were in this group comprising about 18 per cent of all the hypertensive patients. Due allowance for the difficulty in determining heart size accurately in such patients should be made in interpreting this relationship.

In the development of cardiac enlargement in hypertensive patients, the height of the mean pressure, the type of occupation, syphilis, and possibly obesity were probable factors (table 5).

TABLE V
Occupation and Cardiac Enlargement

	Class	Incidence of enlargement Per cent	Incidence in series Per cent
Clerical	1	7.7	12.2
Salesmen, etc	2	17.9	14.6
Professional	3	12.8	15.8
Heavy laborers	4	30.7	21.9
Light laborers	5	15.4	23.1
Unclassified	6	12.8	12.2

ELECTROCARDIOGRAMS

In 48 of the 82 cases, electrocardiograms were reported. Of these, 23 were within normal limits. Six showed only left axis deviation as an abnormality and 19 presented definite abnormalities. The most common finding was inversion of the T-wave in Lead I, which occurred nine times, in three instances associated with inversion of the T-waves in the other two leads, and in one instance, with an inverted T₂ only. Inversion of the T-wave in Leads II and III occurred five times each, but coincided only the three times previously mentioned when all the T-waves were inverted.

The voltage of T-waves was reported low (less than 0.1 millivolt) four times in Lead I, six times in Lead II and three times in Lead III.

The QRS voltage was reported to be less than 0.5 millivolts in all leads in three cases. In the tracing of one of these patients who had had myocardial failure for several years, the QRS complexes were W-shaped and death occurred during his admission. The other two patients had blood pressures that were comparatively low and questionably abnormal. They both had numerous complaints which did not include cardiac pain.

High voltage tracings have been described as more characteristic of hypertension⁸ but none were observed in this series. Low voltage QRS complexes apparently were not related to uncomplicated hypertension.

Three tracings showed deep Q₃ waves which satisfied the usual criteria for significance.⁹ One of the patients gave a history of a severe attack of pain about 10 days before his admission, and his electrocardiogram presented changes suggestive of a healed anterior coronary occlusion and an

acute posterior occlusion. A second patient had a history of precordial pain with cardiac insufficiency for three years preceding his admission and showed also a negative T_3 without left axis deviation or definite cardiac enlargement. It is probable that this patient also had had a coronary occlusion in the posterior portion of the heart. The third patient had had a very high pressure for a number of years, but in this case, the deep Q_3 with an inverted T_3 and left axis deviation may have been the result of a transverse position of the heart in the thorax.

One patient exhibited bundle branch block and one auricular fibrillation. One of the fatal cases showed a coronary occlusion at autopsy and two years previously his electrocardiogram had shown inverted T-waves in Leads I and II. Another patient gave a suggestive history of precordial pain two months before admission and his electrocardiogram showed inversion of T_1 with low voltage of T_2 and T_3 . While only one patient died from an acute coronary thrombosis, the history of several others with their subsequent clinical course, suggested that they had experienced acute attacks probably involving the posterior portion of the heart or small vessels. In any event, characteristic electrocardiographic abnormalities which might not be due to coronary artery disease were not seen in this series.

BLOOD

Polycythemia is sometimes associated with hypertension, and in certain cases the increased viscosity of the blood which results from the increased number of cells may at least be an added factor increasing peripheral resistance. A recent case, not included in this series, exhibited a marked decrease in mean pressure with relief of symptoms when the red blood cells were reduced in number.

When the blood counts of the patients in this series with hypertension were compared with those of a similar sized group of hospital patients without hypertension, the latter group had a greater number with hemoglobin above 16 gm per 100 cc or red blood cells above 5,000,000 per cu mm than the hypertensives. True polycythemia occurred only once in the hypertensive series and the incidence of this condition as a causative factor in hypertension cannot be great. It might be expected that a secondary polycythemia would develop, particularly in those patients with much arteriosclerosis involving pulmonary vessels, but this was not the case, perhaps because of the age group involved.

Anemia may be observed in patients with hypertension, particularly those associated with or due to renal disease. In this series, 31.2 per cent of the patients had a hemoglobin content of less than 14 gm per 100 cc in their blood, while in the control group, the percentage of patients with a hemoglobin below 14 gm per 100 cc was 21.3 per cent. Only eight of the 25 hypertensives with some degree of anemia had manifestations of kidney dysfunction, principally albuminuria and cylindruria (hyaline casts), micro-

scopic hematuria having been reported only once and an elevated N P N (non-protein nitrogen) three times

RENAL FUNCTION

The association of renal disease with hypertension is commonly observed but the etiological relationship of one to the other is usually obscure. Unless there is a history of an acute nephritis or some other renal condition such as polycystic kidney, the signs and symptoms of renal involvement seem to follow the development of hypertension.

The recent investigations of Goldblatt et al¹⁰ and of Wood and Cash¹¹ demonstrate that hypertension of varying degrees of severity may be produced in dogs by constriction of the renal arteries without causing apparent loss of renal function. It is possible that a mild involvement of the kidneys occurs in man which may not affect the function or cannot be detected by our clinical methods, but is sufficient to cause an elevation of blood pressure. At present, such a hypothesis would probably involve a chemical factor causing generalized constriction of the arterioles, and confirmation of such an etiological theory in human beings has been and will continue to be confronted by many technical difficulties and opposing data.

In this series, only two patients gave a history of an acute renal involvement preceding or accompanying the hypertension, one an acute nephritis, and the other a pyelonephritis with obstructing renal calculi.

Various tests of renal function were performed on 56 of the 82 patients and while some show changes which were interpreted as indicating renal dysfunction, not infrequently the kidney failure has been secondary to congestive heart failure. In these cases, if the patient regained his cardiac compensation, the renal function became normal.

In a control group of 63 hospital patients not exhibiting increased blood pressure, the N P N was reported to be greater than 35 mg per cent in 11 or 17.4 per cent, and of these, two had definite arteriosclerosis, one died of a coronary occlusion, one had chronic nephritis and the remainder had other severe systemic illnesses. Determinations of the N P N were reported for 56 of the hypertensive patients, and of these, 14 or 25 per cent were above 35 mg per cent. The highest value was 88.3 mg per cent for a patient who gave a definite history of renal obstruction. It appears that an elevated N P N occurs comparatively infrequently in hospital patients who do not have hypertension or other evidence of cardiovascular involvement.

The blood uric acid was reported on the same patients in the two groups, 44 per cent of the hypertensives had a blood uric acid of 4 mg per cent or above, as compared to 27 per cent in the control series. As indicated in the table (table 6), this is due largely to the number of hypertensive patients with a slight increase in the concentration of uric acid (from 4 to 5 mg per cent) and the disproportion would be even greater if the patients with heart disease as well as the hypertensives were excluded from the control group.

TABLE VI
Blood Uric Acid in Patients with and without Hypertension

Uric Acid mg per cent	Hypertensives per cent	Control per cent
4-5	32.1	17.4
5-6	5.1	7.9
6-7	1.8	1.6
7-8	5.3	0

About half of the hypertensive patients with elevated uric acid did not show any other evidence of renal disease as indicated by the non-protein nitrogen, phenolsulphonephthalein elimination, specific gravity, microscopic examination, and albumin. The four patients with a uric acid above 6 mg per cent also had N P N's above 35 mg per cent, but only five of the 21 with uric acids between 4 and 6 mg per cent had elevated N P N's. Five of the nine cases in which both the uric acid and N P N were elevated died, but in only one of these was death preceded by uremic symptoms and the others represented advanced cardiac failure.

Nine of the 14 patients with N P N above 35 mg per cent had uric acids above 4 mg per cent, five being above 5 mg per cent. This suggests that an elevation of the blood uric acid occurs more frequently in hypertensive renal insufficiency than an elevation of the N P N and the two values do not necessarily vary together. In the control series, only three patients out of 46 with a blood uric acid of less than 4 mg per cent had N P N's above 35 mg per cent, while seven out of 17 patients with blood uric acid above 4 mg per cent had N P N's above 35 mg per cent. The magnitude of increase in either value was not necessarily reflected in the other, thus the highest N P N which was 63 mg per cent was accompanied by a uric acid between 4 and 5 mg per cent, and the highest uric acid concentration, between 6 and 7 mg per cent, was obtained in a patient with an N P N of only 38.9 mg per cent. The uric acid concentration frequently is increased without other evidence of renal dysfunction and in conditions which are not commonly associated with renal damage. When the concentration was elevated in patients with hypertension, it probably indicated decreased kidney function and when higher concentrations occurred, the prognosis was unfavorable. Five of seven hypertensives with uric acid above 5 mg per cent died and the other two had evidence of recent coronary occlusions which they survived. The N P N in both of these latter cases was normal and it is suggested that the hyperuricemia was extra-renal in origin. Dependence on the estimation of the retention of one chemical substance in the blood is obviously very unsatisfactory for detecting a reduction in renal function in hypertension.

The elimination of phenolsulphonephthalein injected intramuscularly in two hours was estimated in most of the control series along with uric acid

and N P N In only one case out of 16 in which the uric acid was above 4 mg per cent, was the P S P below 40 per cent This method of performing the examination apparently gives very little information in lesser degrees of renal failure

The highest specific gravity reported for any specimen of urine during the patient's stay in the hospital was recorded In 11 cases the specific gravity was less than 1 020 but in five of these, no albumin or abnormal findings in the urine sediment were reported Six showed varying amounts of albumin, three showed hyaline and granular casts and two showed some nitrogen retention in their blood

In the control group, the urine of only nine out of 76 patients showed a specific gravity below 1 020 Five of these had hypertension or arteriosclerosis, three had albuminuria and two moderate nitrogen retention The opinion has frequently been expressed by other investigators that concentration tests are of particular value in evaluating kidney function, but good cooperation on the part of the patient is essential In our experience, this is not always obtained on general wards that can not be closely supervised

Twenty-one in the hypertensive group showed varying amounts of albumin in their urine with a specific gravity of more than 1 020 No attempt was made to correct for the albumin

Routine determinations of urea or creatinine clearances were not made in this series It is generally conceded that such studies are of more value than single estimations of one of the nitrogenous blood constituents but even the clearances are subject to wide variations and require considerable supervision The routine performance of various laboratory examinations by technicians without proper evaluation by the clinician of the conditions under which the examination was made or the proper control of the patient may give data that are more confusing than helpful A limited number of well conceived, properly performed procedures are of more value in the general study of a patient with hypertensive heart disease than many random examinations less carefully controlled

DEATHS

In this small series of hypertensives, there were only eight deaths, or a mortality of 9 7 per cent, with an average age at death of 53 years as compared to the whole discharge group in which there were 91 deaths or a mortality of 5 6 per cent and an average age at death of 52 years In this latter group, the average age at death of the colored patients was 46 years and of the white patients 53 8 years

One of the patients, aged 42 years, had had headaches all his life as had his mother During the War, he was an aviator but did not go overseas He had malaria from 1919 to 1922 and had not felt well since In 1931 when first examined, his blood pressure was 138 systolic, 86 diastolic, his retinal and peripheral vessels showed some thickening but there was no evidence of renal or heart involvement

In 1933 his blood pressure was 200 systolic, 128 diastolic. His headaches were more frequent and associated with nocturia.

In 1935 he was admitted to the hospital with congestive heart failure which improved. His blood pressure was 215 systolic and 140 diastolic. The N P N was 43.7 mg per cent on admission but dropped to 33.3 mg per cent as the signs of heart failure disappeared. About one month after admission, he was feeling very well when he suddenly complained of a sensation of acid being poured over his face and left side. He soon developed unconsciousness and died.

The postmortem examination revealed a small hemorrhage in the pons, and unusually marked sclerosis of the vessels of the Circle of Willis. The heart showed hypertrophy of the left ventricle with a small area of healed infarction. The kidneys were about normal in size, the larger vessels showed sclerosis, the glomeruli were large and some showed hyalinization.

The second patient, aged 64, was admitted in an unconscious state and died within 72 hours. A history was not obtained but he presented evidence of a right-sided hemiplegia with a hypertension of 178 systolic and 120 diastolic. The blood N P N was 70.5 mg per cent, uric acid 7.9 mg per cent and the urine showed a few red blood cells, many hyaline and granular casts and 1-plus albumin.

The postmortem examination failed to reveal a localized cerebral lesion of any kind but the brain and ventricles were filled with fluid resembling the so-called alcoholic wet brain. The cerebral vessels were definitely sclerotic. The kidneys were somewhat small with adherent capsules and decreased cortical width. Certain areas showed fibrosis with complete obliteration of the glomeruli while others were distended. The heart was enlarged and showed swelling of the muscle fibers with considerable interfibrillar connective tissue. Death apparently was due to renal failure.

The third patient was 45 years old and colored. He had worked as a laborer until a few weeks before his first admission in 1933 at which time he had congestive heart failure. The highest blood pressure obtained during his hospitalization was 148 systolic and 105 diastolic. His renal function was good. He was admitted in extremis about two years later and at autopsy the heart was enlarged and presented a saucer-like fibrous dilatation near the apex and a fresh mural thrombus beneath an area on the left ventricular wall in which the musculature was necrosed and infiltrated with polymorphonuclear cells. The kidneys were small and contracted showing cellular infiltration and intertubular fibrosis. The larger vessels were definitely sclerotic and an occasional glomerulus was obliterated.

The fourth patient was a Spanish-American War veteran, 66 years old. He had had a diagnosis of high blood pressure and heart disease for many years but had been able to work as a steam engineer until three months before his admission. He gave a history of a recent intestinal hemorrhage which had resulted in a profound anemia and apparently heart failure.

The postmortem revealed no tumor of the gastrointestinal tract but an area near the splenic flexure with many bleeding points from distended veins. The aorta above the sinuses of Valsalva down to the iliac bifurcation was the site of a severe arteritis with loss of elastica, irregular fibrosis, ulceration, hemorrhage into the wall with fatty change, and calcareous plaque formation. The heart showed fragmentation, swellings and granularity of the muscle fibers. The kidneys showed dilated tubules filled with detritus with focal reaction and fibrosis about some glomeruli, although the tubular involvement was the most striking. The liver showed a perlobular round cell reaction and evidence of cell degeneration which was called an infectious hepatitis. There was a small adenoma in one adrenal. It was felt that death was due to an infectious aortitis with the intestinal hemorrhage as contributory.

The fifth patient was a World War veteran, aged 45. His only illness during service was trench mouth and he had been well since discharge until 1929, when he

had had kidney stones for which he was cystoscoped. It is not known what his blood pressure was then or the exact location of the stones, but from that time he had not been well. In 1935 he was treated in another hospital for nephritis and subsequently in this hospital where he died. Because of the high blood pressure, evidences of renal insufficiency and cerebral symptoms, a diagnosis of uremia was made. Postmortem examination was refused but this case was considered to be a chronic nephritis with secondary hypertension and uremia.

The sixth patient was 74 years old and had served as a Medical Officer during the World War. He was admitted because of senile psychosis and congestive heart failure, apparently dying of bronchopneumonia. Postmortem examination revealed the usual changes of arteriosclerotic heart disease in the heart, blood vessels and kidneys.

The seventh patient was a World War veteran, aged 45. He had known of his hypertension for at least five years and recently had complained of marked cardiac insufficiency. He was semi-stuporous when admitted, had an extremely high blood pressure with papilledema and numerous areas of retinal exudate. Kidney function as evidenced by the blood chemistry and urinary findings was normal. This was considered a malignant hypertension with cerebral edema. Postmortem examination was not permitted.

The eighth patient was a World War veteran, aged 41. He had had scarlet fever, diphtheria and empyema in early childhood, typhoid fever at age 15, and during the War received a gunshot wound and a burn with liquid fire. He was also confined in a German prison camp for four months during which time he first noticed dyspnea and edema. Since discharge from the Army, he had been able to do some work as a salesman until about 1928, but always had some cardiac insufficiency. On admission to the hospital in 1934, he was in severe congestive heart failure and made very little improvement during his 18 months hospitalization. Although he presented evidence of renal insufficiency, this was considered a result of his myocardial failure. An autopsy was not performed. The diagnosis was hypertensive heart disease with congestive failure.

Three of the patients, therefore, were over 60 years of age, one died of bronchopneumonia with congestive heart failure, one apparently died of uremia while the third died following severe intestinal hemorrhages and had a marked aortitis, probably infectious in origin. The remaining five patients were between 37 and 47 years of age at the time of their death and a common factor that may have been responsible for their severe and comparatively short course is not apparent. The immediate family histories indicated a fairly high familial tendency to cardiovascular disease. Renal injury appears to have been an early factor in one case while marked cerebral vascular changes may have been important in two other cases. Only one patient died of an intracranial vascular accident. The two patients that died of congestive heart failure presented evidence of myocardial damage from coronary artery disease.

SUMMARY AND CONCLUSIONS

The incidence of hypertension in 1369 veterans was 6 per cent.

There was a comparatively greater incidence of hypertension among the negro patients whose average age was about five years younger than that of white patients.

A high proportion of the negro patients have syphilis which may account for the early and more serious involvement

The morbidity history during service and subsequently, did not implicate any particular infection as a precursor of hypertension

Involvement of the retinal arteries with a sclerotic process was observed four times before the blood pressure became chronically elevated. This suggests involvement of the cerebral circulation as a factor in the causation of some cases of hypertension

Psychotic and severe psychoneurotic manifestations were found in 13 per cent of the cases. Four patients had suffered cerebral trauma. It is suggested that certain chronic emotional reactions and brain injuries may influence the central regulation of blood pressure

About one-third of the patients with hypertension had been obese at some time in their lives as evidenced by body weight over 200 pounds

A definitely greater incidence of cardiovascular-renal disease was reported in the immediate families of hypertensive subjects than in a control group

The more laborious physical occupations were the most common means of livelihood for about 45 per cent of the group, and the average age of the patients was lower than the professional and clerical groups

Cardiac enlargement was apparent in about one-third of the patients. The height of the mean pressure, occupation, syphilis, and possibly obesity, were the most prominent factors associated with enlargement

Typical electrocardiographic changes that are not characteristic of coronary artery disease were not noted

Polycythemia was present in only one hypertensive patient while one-third showed some degree of anemia

Examination of renal function in 56 patients revealed abnormalities of one or more findings in approximately 60 per cent of the cases. A slight rise in the blood uric acid occurred most frequently

There was very little correlation between the uric acid and the non-protein nitrogen values

Congestive heart failure was frequently responsible for renal failure

Death occurred in eight cases or approximately 10 per cent

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CASE REPORTS

TULAREMIC MENINGITIS

Report of Case with Postmortem Observations *

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THE histopathology of tularemia is adequately described in the literature notwithstanding the few reports of postmortem examinations. But because there are few reported necropsies the pathology of the disease is of particular interest in regard to the distribution of the lesions. Last year Bernstein was able to collect only 18 necropsies and to these he added three of his own. We have reviewed these cases and three additional reports by Beck and Merkel, Amoss and Sprunt, and Kavanaugh to determine the distribution of the lesions. This study was prompted by the occurrence of a fatal case of tularemia which was diagnosed at autopsy, and in which the outstanding feature was meningitis. Because there is only one report that describes the pathology of tularemic meningitis and furthermore because in our case lesions were observed in organs where they have not been previously observed, this case is of unusual interest.

CASE REPORT

A negro girl, aged 12, was admitted to the hospital on the third day of her illness. The history was obtained from the father who had been separated from his daughter and it is therefore brief and incomplete. No reason for the lesion on the forearm could be obtained.

The present illness began with fever, abdominal pain and headache, followed by nausea and vomiting 24 hours later. The patient appeared very ill, was semiconscious and the skin was hot and dry. Temperature was 105.8° F, pulse 106, and respirations 24. Blood pressure was 140 systolic, 100 diastolic. The lips were parched and the tongue furred in the center and glazed at the margins. Pharynx and tonsils appeared congested. Impaired resonance was elicited over the right pulmonary apex and scattered râles were heard at the right base. The abdomen was distended, tympanitic and diffusely tender, especially over the cecum and spleen. On the flexor surface of the left forearm near the wrist was an ulcer 3 cm. in diameter, which was surrounded by several small vesicles. The reflexes were normal. The clinical impression was typhoid fever.

Pyrexia was continuous during the eight days of observation, between 103 and 106.2° F, pulse increased from 106 to 160 and respirations from 26 to 40. Culture of the throat proved negative for diphtheria, two stool cultures failed to reveal the *Bacillus typhosus* and the Widal reaction was negative. Total leukocyte count was 8,700, with polymorphonuclear leukocytes 65 per cent, small lymphocytes 33 per cent and large lymphocytes 2 per cent. The red blood cell count was 4,100,000 and the

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hemoglobin estimated at 85 per cent. The tuberculin skin test was negative. On the fifth day of hospitalization the neck was stiff and Brudzinski's and Kernig's signs became positive. The following day semiconsciousness was followed by coma. The abdomen became rigid. Tuberculous meningitis was now thought to be a possibility, although the diagnosis of typhoid was not relinquished and an intestinal perforation was considered. The cerebro-spinal fluid revealed 114 cells per cu mm, was under 18 mm Hg pressure but yielded negative tests for globulin. The Wassermann reaction on the spinal fluid was negative. The next day the cell count was 200 and the pressure 22 mm Hg. Prolonged search in films from both specimens failed to reveal tubercle bacilli. Blood and spinal fluid cultures remained sterile and the blood serum failed to agglutinate the organisms of undulant fever. Coma continued and death occurred the eighth day of hospitalization or the tenth day of her illness.

Necropsy

A necropsy was performed nine hours after death.

The body was that of a wasted negro female child. An ulcer 3 cm in diameter with a necrotic base was observed on the palmar surface of the left forearm just above the wrist. In the pia-arachnoid innumerable minute yellow foci were regularly distributed but barely visible over all surfaces of the brain. The cerebro-spinal fluid was yellowish. The cord was not examined.

The peritoneal cavity contained about 400 c c of clear light yellow fluid. A small amount of fibrinous exudate was seen on the serosa of the appendix, otherwise the peritoneal surfaces were smooth and glistening. The right pleural cavity contained some 25 c c of turbid fluid and the surfaces were dull and congested. The left pleural cavity contained a like amount of clear fluid and the surfaces were smooth and glistening. In the middle anterior part of the upper lobe of the right lung a firm airless area about 5 cm in diameter was palpated. This, on section, was wedge-shaped, granular and pink but the central part 1 cm in diameter was yellow and caseous. Otherwise both lungs were alike. They were heavy and soggy but crepitant. Cut surfaces were wet, yielded much frothy fluid and were mottled with slightly raised reddish areas, more numerous in the right lung. The mucosa of the trachea and bronchi was congested. The tracheo-bronchial lymph nodes were enlarged to 2 cm in diameter and an occasional small yellow focus was seen against the moist gray background.

Through the capsule of the liver, especially near the inferior border, numerous minute yellow areas were visible and a few similar foci were seen on the cut surface. The spleen was a little enlarged, weighing 130 grams. Its capsule was studded with numerous yellow spots. Similarly the cut surface was studded with round yellow foci, the largest about 0.3 cm in diameter. The mucosa of the appendix in its distal third was necrobiotic and ulcerated. The lymph nodes of a group near the cystic duct were slightly enlarged and several contained small caseous foci. Some three or four left axillary lymph nodes had attained a size of 2 cm in diameter each and were filled with caseous areas, the largest 1 cm in diameter. No noteworthy changes were noted in the other viscera.

Microscopic Examination

The floor of the ulcer of the forearm showed necrosis which involved the subjacent subcutaneous tissue. In the necrotic material shadows of macrophages were seen. The tissues immediately around the area of necrosis were infiltrated with de-

generating polymorphonuclear leukocytes and lymphocytes. Ten representative sections from the brain were studied. In the extreme cortex of the cerebrum and in the submeningeal part of the pons there were numerous minute, rather wedge-shaped collections of small round mononuclear cells and an occasional polymorphonuclear leukocyte. Centrally in the foci was much nuclear and cytoplasmic detritus. The small mononuclear cells displayed pyknotic nuclei. The cytoplasm while generally scant was occasionally increased and foamy, thus suggesting microglial origin. The brain tissue around the foci was slightly rarefied. Many of these aggregates were



FIG 1 Section from meningeal surface of pons. Note the wedge-shaped area infiltrated with small mononuclear cells. This focus is confined within the substance of the brain, however, there is a diffuse meningitis. $\times 240$

confined within the substance of the brain, but the larger ones extended into the leptomeninges (Figures 1 and 2). The leptomeninges were furthermore diffusely infiltrated with small round cells and polymorphonuclear leukocytes. A tendency to focal coagulation was noted in the infiltrate. The exudate in the meninges extended a short distance along the vessels into the submeningeal tissue. Beneath the ependyma of the lateral and fourth ventricles smaller foci similar to those of the cortex and pons were found. The ependyma remained intact. Endothelial swelling and proliferation were noted in some of the vessels nearby. No lesions were observed deep in the

brain The diffuse infiltration of the meninges was noted between the folia of the cerebellum and here and there were deposits of coagulated serum Slight rarefaction of the submeningeal part of the cerebellum occurred, but no inflammatory foci were seen In the choroid plexus there was nothing noteworthy

In the thymus reticular-cell hyperplasia and occasional giant cell formation were noted The airless area in the right lung was caused by a pneumonic infiltration The alveoli were filled with fibrin which enmeshed a few large mononuclear cells, lymphocytes and nuclear detritus Caseous necrosis of the lung and exudate occurred centrally Similar scattered smaller areas and many necrobiotic areas of local hemoi-

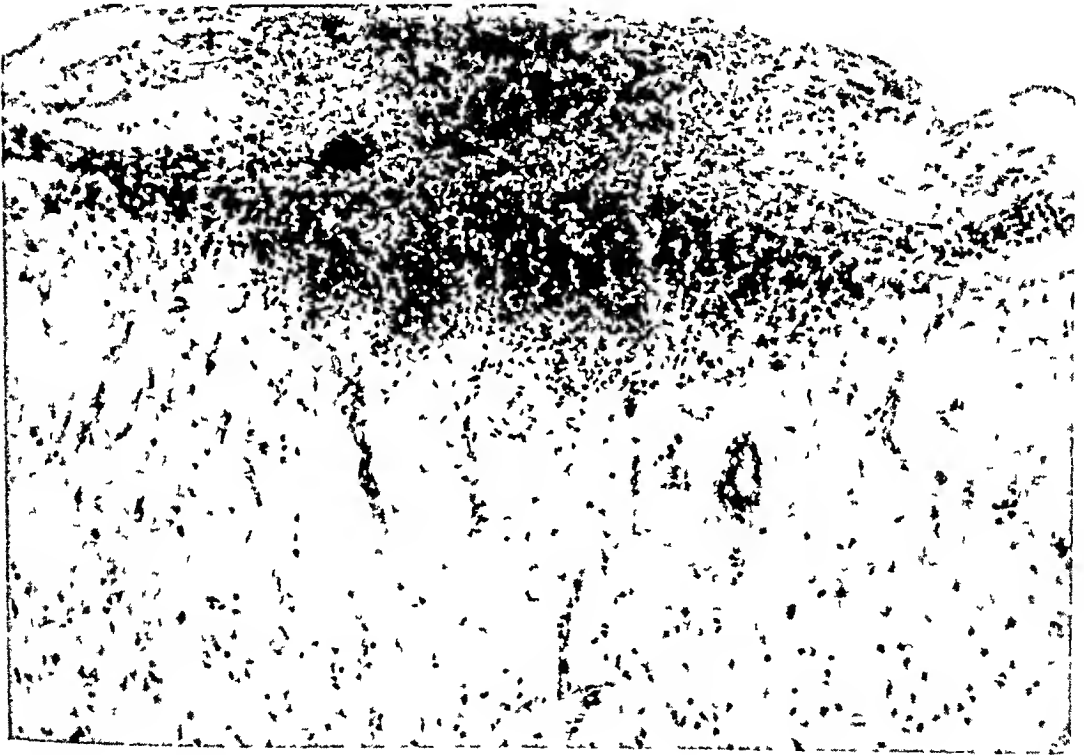


FIG 2 Section from meningeal surface of cerebral cortex The lesion is similar to figure 1, but extends into the meninges $\times 240$

rhage and edema were seen in other sections from the lungs In the liver the Kupffer cells appeared prominent Numerous round caseous foci without cellular detail were encountered Necrotic areas of varying size were distributed in the splenic pulp but were more often observed in the lymph nodules Macrophages with indistinct outlines could be seen in the periphery of some of these foci An occasional necrotic focus extended into and some through the capsule A thin sheet of exudate of fibrin, nuclear detritus and an occasional recognizable macrophage covered the spleen Also there was diffuse hyperplasia of the reticulo-endothelium and the sinuses were congested

Coagulation necrosis of minute aggregates of large mononuclear cells was noted

in the medulla and reticular zone of the suprarenal. The endometrium of the uterus was diffusely infiltrated with macrophages, some of which were collected in small groups which appeared necrobiotic (figure 3). Many macrophages were filled with engulfed particles of nuclear debris. In the distal end of the appendix the mucosa and the submucosa were infiltrated with many large mononuclear cells laden with nuclear debris. There was confluent focal necrosis of the mucosa with ulceration. An exudate of fibrin and macrophages was present on the serosa (figure 4). In the axillary, tracheo-bronchial and supra-pancreatic lymph nodes there was diffuse

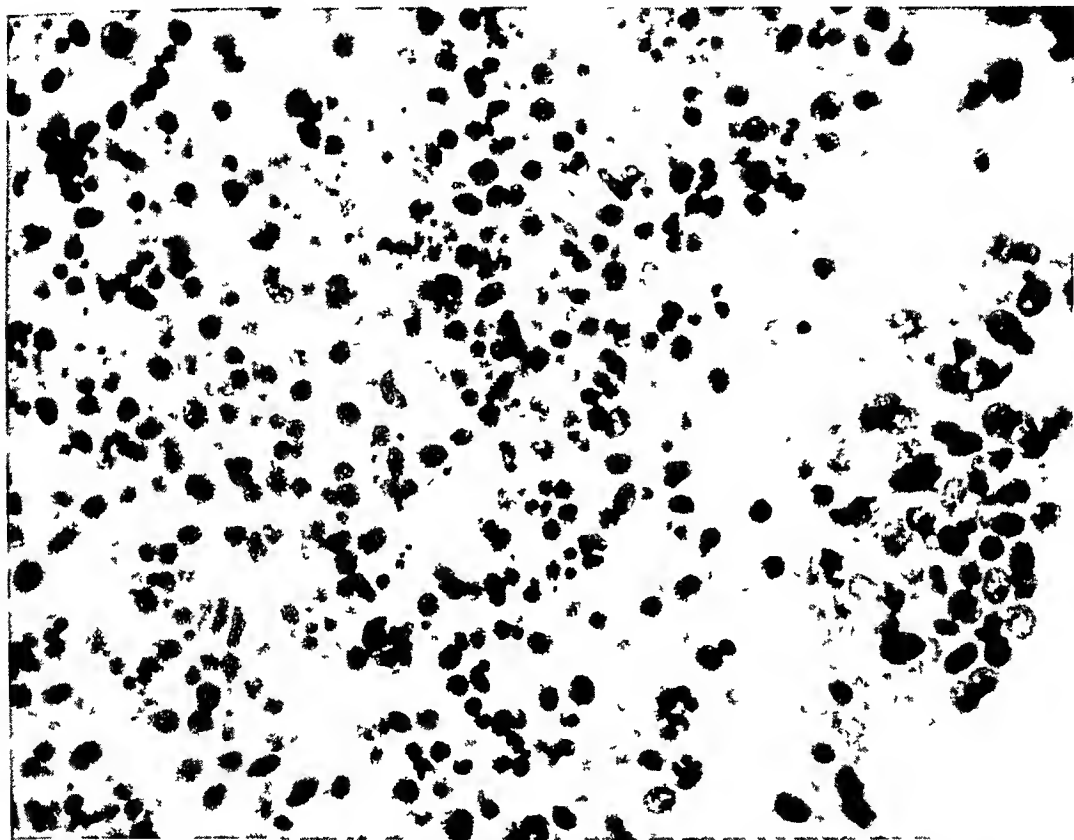


FIG 3 Section from endometrium. Disorganization of the endometrium and infiltration with numerous macrophages, some engulfing nuclear detritus. There is a tendency to grouping of these cells. $\times 1000$

reticulo-endothelial hyperplasia and the sinuses were crowded with macrophages. Necrotic foci without cellular detail were noted. The largest areas occurred in the axillary nodes.

No acid fast organisms could be found in sections from the brain, lymph nodes, lungs and spleen. Routine sections from the heart, aorta, thyroid, kidney, bladder, ovary and pancreas revealed no noteworthy changes. Blood serum, obtained at necropsy and examined by the laboratory of the Georgia State Board of Health, agglutinated *Bacterium tularensis* in dilutions from 1:640 to 1:1280.

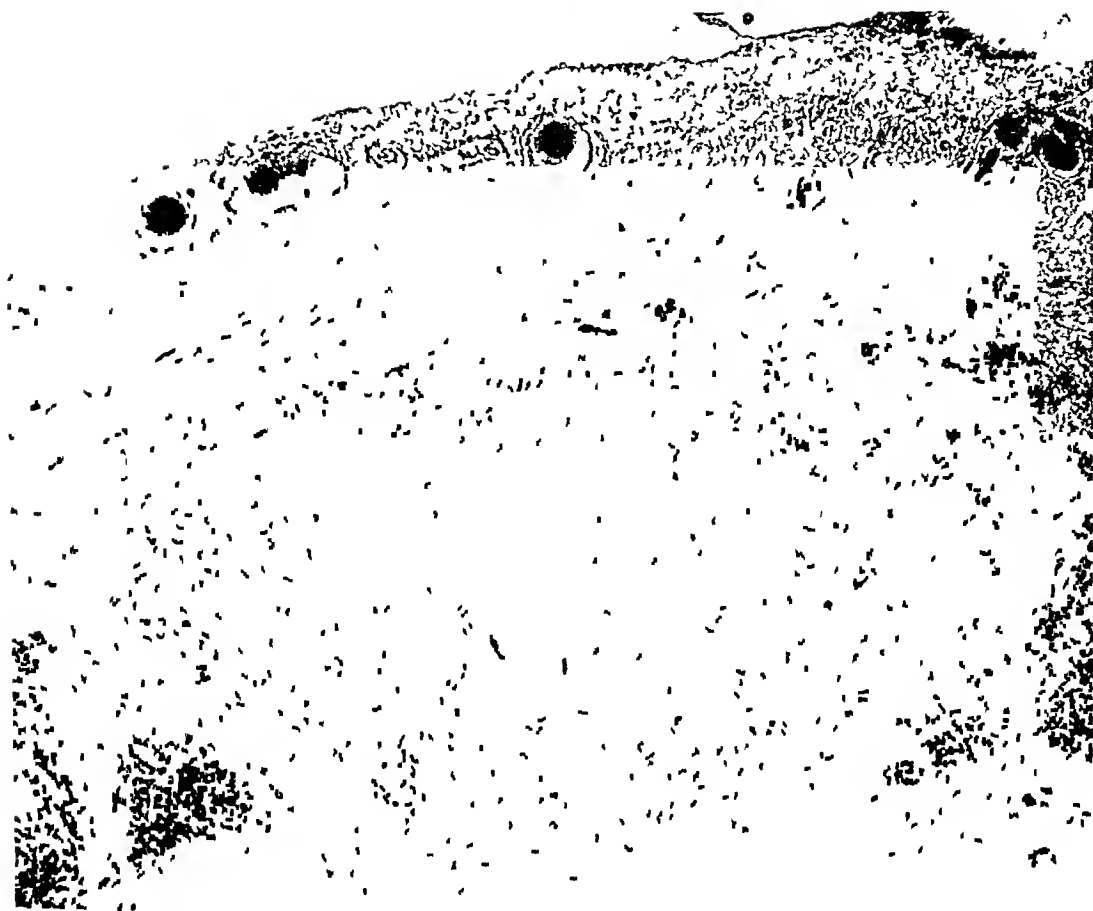


FIG 4 Section from proximal third of appendix. Note the necrosis and ulceration of the mucosa. Dense infiltration with macrophages. $\times 75$

COMMENT

In this case the lesions of the central nervous system are of especial interest both from the clinical and pathologic standpoint. Meningeal symptoms have been noted not uncommonly in patients with tularemia, but the existence of tularemic meningitis was first demonstrated by Haizlip and O'Neil. In their fatal case with meningeal symptoms the brain and cord were not examined at necropsy, but injection of the spinal fluid produced tularemia in a guinea pig. In the literature we found only one description of the histopathology of tularemic meningitis, the case reported by Bryant and Hirsch. They described lesions in the meninges, submeningeal brain tissue, ependyma, subependymal tissues and choroid plexus. The involvement of the brain was considered an extension from the lesions of the meninges. Our observations differ from theirs in that isolated foci were seen within the confines of the brain (figure 1). The difference is probably due to the fact that our case represents an earlier stage in the pathology of the disease, their patient died on the sixteenth day of illness while ours died on the tenth day. It would seem from our observation that the meningitis occurred secondary to tularemic encephalitis. Lesions in the brain

without meningitis have been reported by Hartman. In a case of tularemia he found soft, grayish yellow, necrotic or hemorrhagic areas from 0.5 to 3 mm in diameter in the corpus callosum, basal nuclei, pons and the adjacent tissue. Microscopically these lesions were characteristic of those produced by the *Bacterium tularensis*. The manner of production of tularemic meningitis is probably the same as in tuberculous meningitis. Rich and McCordock have shown that tuberculous meningitis has its origin in the discharge of bacilli into the cerebro-spinal fluid from adjacent older caseous tuberculous foci. In the 24 necropsies previously reported, the brain and meninges were examined in only four cases. Two of these exhibited the lesions described above. The case of Foulger, Glazer and Foshay showed no noteworthy changes in the brain and meninges, while Palmer and Hansmann described a minute pontile hemorrhage and noted elevations on the pia-arachnoid due to several layers of fatty endothelial cells.

Our report is of further interest because lesions were observed in the appendix, thymus and uterus. In the reported 24 necropsies the inflammatory reaction of tularemia was observed in the spleen in 21, lungs in 20, lymph nodes in 20, liver in 19. Involvement of the other organs is rare. Our case exhibited microscopic foci of necrosis in the suprapneural. Francis and Callender have previously noted lesions here. Baidon and Berdez described congestion and swelling of Peyer's patches and solitary follicles of the intestine, and numerous small yellow patches were noted in the mucosa of the stomach and of the small and large intestine, but they did not describe these lesions microscopically. Simpson, and Bunker and Smith observed congestion of the mucosa of the stomach and intestines. Foulger, Glazer and Foshay described the lining of the entire gastrointestinal tract as dull, dirty, grayish pink with engorgement of the blood vessels. Microscopically they observed a diffuse and focal lesion on the serosal surface which was characteristic of tularemia. In Bernstein's first case scattered punctate hemorrhages were seen in the gastric mucosa, in the second, ulceration of the esophagus was noted, in the third, a necrotic focus occurred in the tonsil. Beck and Merkel described grossly and microscopically small ulcers of the stomach, duodenum, ileum and ascending colon which showed the typical necrosis and leukocytic infiltration. The cellular infiltration was confined to the mucosa. There was a fatal case of the typhoid form caused by the ingestion of rabbit. In our case there was a distinctive tularemic appendicitis with local peritonitis which was recognized grossly and confirmed microscopically. No other lesions were seen in the gastrointestinal tract. Sections from the proximal two-thirds of the appendix revealed no lesions. Here then, we have a focal involvement of the appendix which could be hematogenic, yet the possibility of a primary intestinal lesion should be considered. As mentioned above, the only case that exhibited ulcers of the stomach and intestine was reported by Beck and Merkel and in this instance the infection was caused by ingestion of rabbit. It is not unreasonable to think that there may be two sites of inoculation, especially since the person who dresses the infected animal usually eats it. This would explain the fulminant course of some cases because of easy hematogenous dissemination from the intestinal tract. That it is not necessary for the ingested organisms to produce a gastrointestinal lesion is evidenced by the report of Amoss and Sprunt. In their case no gastrointestinal lesions were found although the disease was contracted by ingestion of rabbit. The ap-

pendicitis and serositis of the spleen explain the abdominal tenderness in these regions and the rigidity that developed later

Involvement of the thymus and uterus has hitherto not been reported. While we observed no foci of necrosis in the thymus, there was hyperplasia of the reticulum, a change also noted in the liver, spleen and lymph nodes. The thymus was the only site where giant cell formation occurred. In the uterus of our case there was diffuse endometritis. Kavanaugh observed three patients who contracted tularemia during pregnancy and were delivered of normal babies during the height of infection. In one case labor was premature. Nor did coexisting tularemia endanger pregnancy in the patient of Bowe and Wakeman. A lesion of the uterus probably occurs rarely yet is one to be considered when pregnancy is complicated with tularemia.

SUMMARY

A case of tularemic meningitis is described.

The meningitis is apparently secondary to hematogenic encephalitis.

The distribution of the lesions of the reported fatal cases of tularemia is summarized and involvement of the uterus, thymus and appendix is described.

The possibility of double infection, by way of the skin and gastrointestinal tract, is suggested.

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RENAL AMYLOIDOSIS WITH CLINICAL FINDINGS SUGGESTIVE OF POLYCYSTIC KIDNEY *

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SINCE the beginning of the aseptic era in surgery, general amyloidosis appears to be common only in sanatoria for the care of tuberculous patients. Dixon reported 100 cases of pulmonary tuberculosis, 70 of whom had amyloidosis. Perla and Gross reported 100 cases of amyloidosis out of 112 cases of pulmonary tuberculosis, and Saleeby 41 out of 50 cases. In a series of 579 autopsies at Glen Lake Sanatorium, 109 cases of amyloidosis were discovered, an incidence of 19 per cent. The incidence is less than is usually quoted by the various authors from other sanatoria. Rosenblatt found amyloidosis in 24.4 per cent of 451 necropsies and Perla and Gross in about 25 per cent of 400 post mortems.

Of our 109 cases of amyloidosis, the following was in every respect the most unusual.

CASE REPORT

At the age of 16 years, the patient had a cervical adenitis, at 18, cough, expectoration containing tubercle bacilli, high fever, and a pulmonary hemorrhage. Upon his admission to the Sanatorium in September 1921, shortly after the above symptoms were noted, fibroid pulmonary tuberculosis of the right middle and the left upper lobe was present as well as cavitation in the left upper lobe with a small spontaneous pneumothorax at the apex. The urine showed no abnormalities, and his blood pressure was 116 systolic and 60 diastolic. In 1922, a diagnosis of intestinal tuberculosis was made. Sufficient retrogression of both his pulmonary and intestinal lesions occurred so that on November 1, 1924, he was discharged with his tubercu-

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losis considered arrested. He remained in good health for three years and had, during this interval, many urinalyses which showed no abnormal findings.

In 1927, albumin was found in the urine in addition to hyaline, granular, and waxy casts. In February 1928 he developed an upper respiratory infection associated with pain in the right lumbar region. His blood pressure was 153 systolic and 105 diastolic. His urine contained 3 plus albumin and many casts, phenolsulphone-phthalein excretion was 22.5 per cent, blood urea 38 mg, and non-protein nitrogen 77 mg per cent. In January 1930, he was confined to bed for four days because of an acute upper respiratory infection, his right kidney was palpable and tender at this time. He had many recurrences of these respiratory infections and "kidney pains." In February 1932, the lymph nodes on the right side of his neck became palpable, enlarged, and eventually suppurated with the formation of a sinus which healed after four months.

Between 1930 and 1932 his blood pressure varied between 130 systolic and 88 diastolic and 148 systolic and 102 diastolic. In May 1932, it was 128 systolic and 80 diastolic. His urinalysis showed specific gravity 1.017, albumin 3 plus, a few hyaline casts with fat droplets and very occasional granular casts. The hemoglobin was 87 per cent (11.98 gm) and red blood cells 4,600,000.

Following an acute upper respiratory infection in February 1934, the blood pressure was 144, and the urine analysis showed the following: specific gravity 1.017, albumin 4 plus, a few hyaline and granular casts. Although the patient was known to have had a persistent and usually heavy albuminuria for about six years, and on several occasions a slight transient edema, he had no enlargement of his liver or spleen nor demonstrable active tuberculosis at this time. Because of the urinary findings, a diagnosis of amyloidosis was made.

An acute upper respiratory infection in October 1934 was followed by repeated vomiting for several days, so that fluids could not be retained. Urine showed albumin 4 plus, erythrocytes, many leukocytes, and many casts, blood non-protein nitrogen 39 mg and urea nitrogen 27.3 mg per cent. Blood pressure 126 systolic and 90 diastolic. No edema was present. This episode marked the onset of the terminal phase of his illness. Upon advice, he resigned his position which he had held since 1925.

He was hospitalized on October 25, 1934. His blood pressure was 126 systolic and 90 diastolic. Urinalysis showed specific gravity 1.012, albumin trace, white blood cells 10-15, red cells 1-2 per high power field. Non-protein nitrogen was 39 mg, blood urea nitrogen 27 mg per cent. There was a gradual drop in urinary output, and on November 1 and 2, his output was only 100 cc and 80 cc respectively. On the day of the low output his blood urea nitrogen was only 18.5 mg and creatinine 1.9 mg per cent. For the previous three days his intake was never below 2000 cc and on November 1 reached a maximum of 2950 cc. On November 2, the patient was drowsy, and his speech was retarded. On November 3, he was given two intravenous injections of 25 per cent dextrose in normal saline, 300 cc each, and on that day his output increased to 325 cc. The Karell treatment was instituted on the same day with 210 cc of skimmed milk every six hours. November 4, the 24 hour output reached 580 cc. On November 6, the Karell treatment was discontinued, and the patient was allowed 1000 cc of fluids. After this time, urinary suppression caused no further concern so that by November 9, his output was 1250 cc and for the first time exceeded his intake (figure 1). During the period of urinary suppression and forced fluids, there was no edema and the feces were large, soft, and not increased in number.

About November 1, there was a distinctly palpable mass in the right upper quadrant of the abdomen. This was considered to be the right kidney by most observers, although a surgical consultant considered that an upper abdominal malignant growth, particularly carcinoma of the proximal portion of the transverse

colon, should be considered. This mass remained palpable for about one month. A cystoscopic examination showed a pelvic deformity of both kidneys which very strongly suggested polycystic disease (figure 2). Because of the roentgen findings simulating polycystic disease of the kidneys and because one kidney was palpable, the diagnosis of renal amyloidosis or chronic glomerulo-nephritis, with nephrotic component, was changed to polycystic disease of the kidneys.

On November 27, the patient developed an acute, non-contagious parotitis on the right side. This was accompanied by fever, elevation of pulse rate, and toxemia.

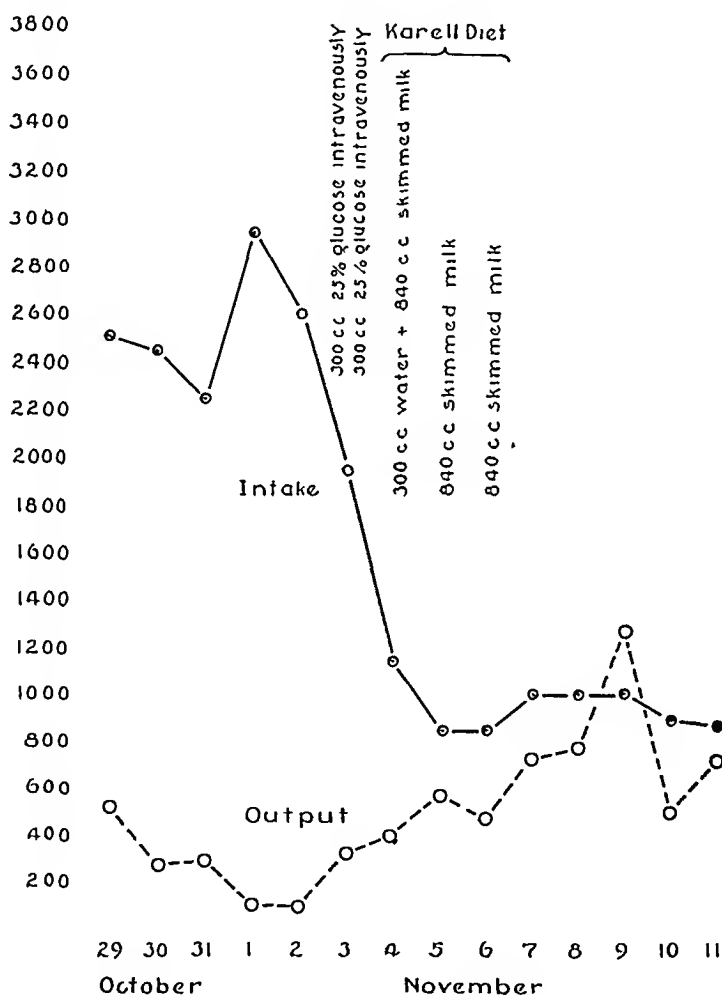


FIG 1 Chart of the patient's intake and output showing the change after the Karell diet

Four days prior, the first evidence of edema in the ankles was noted, but diminished on a salt free diet. On December 7, the parotid swelling had greatly diminished and soon disappeared. The blood pressure was 150 systolic and 96 diastolic. The right kidney, which could be felt as low as the umbilicus a month previously, had greatly diminished in size.

On November 18, an intravenous phenolsulphonephthalein showed no dye excretion within two hours. This was repeated on November 26 with the same result. On November 28, the blood urea nitrogen was 49.6 mg and the creatinine 3.0 mg per cent.

On January 3, 1935, the hemoglobin was 50 per cent, Sahli, in contrast to 75 per cent on entry. The blood urea nitrogen was 50.7 mg per cent. The patient was put on 0.5 gram of reduced iron three times a day. On February 16, the hemoglobin had increased to 72 per cent and one month later, with the patient near death, it was 62 per cent although iron had been discontinued for two weeks.



FIG 2 Retrograde pyelogram showing the widened and elongated renal pelves and calices suggesting polycystic disease of the kidneys

Edema became a troublesome and an increasing feature of the patient's illness after February 14. On March 5, stool specimens contained large amounts of red blood. On March 13, the blood pressure was 180 systolic and 110 diastolic. Urinalysis showed specific gravity 1.009, albumin trace, white blood cells 8-10 per high power field. On March 24, he began to vomit bright red blood and continued to do so for several days. His edema became more marked, and there was a gradual rise

of the blood urea nitrogen (highest 59.3 mg per cent) Marked fatigue, vomiting, and signs of uremia increased until April 15, 1935 when death occurred

Autopsy Report Postmortem examination revealed a marked generalized edema, a non-tuberculous fibrinous pericarditis, and a decubital ulcer over the sacrum

The lungs contained numerous irregularly scattered, healed, calcified nodules varying in size from 2 to 6 mm The apices were puckered and fibrotic Three thin



FIG 3 Photograph of the right kidney showing the enlarged pelvis and the narrowing of the renal cortex The shape of kidney pelvis and the narrowing of the renal cortex are evident

walled cavities, each 7 mm in diameter, were situated in the left apex, these were filled with thick white pus in which no organisms were found

The spleen weighed 112 grams, the liver 1500 grams They showed no evidence of disease The right kidney was situated 8 cm lower than the left and the ureter was correspondingly shorter The right kidney weighed 85 grams, the left 95 grams The parenchyma was firm, waxy, and the distinction between the cortex and medulla had almost disappeared The pelves, although not distended, appeared larger than normal and extended nearer the poles of the kidneys than is usual (Figure 3)

Microscopic examination In the left lung there are several minute calcified nodules surrounded by giant and epithelioid cells and lymphocytes. The cavity walls show a similar activity.

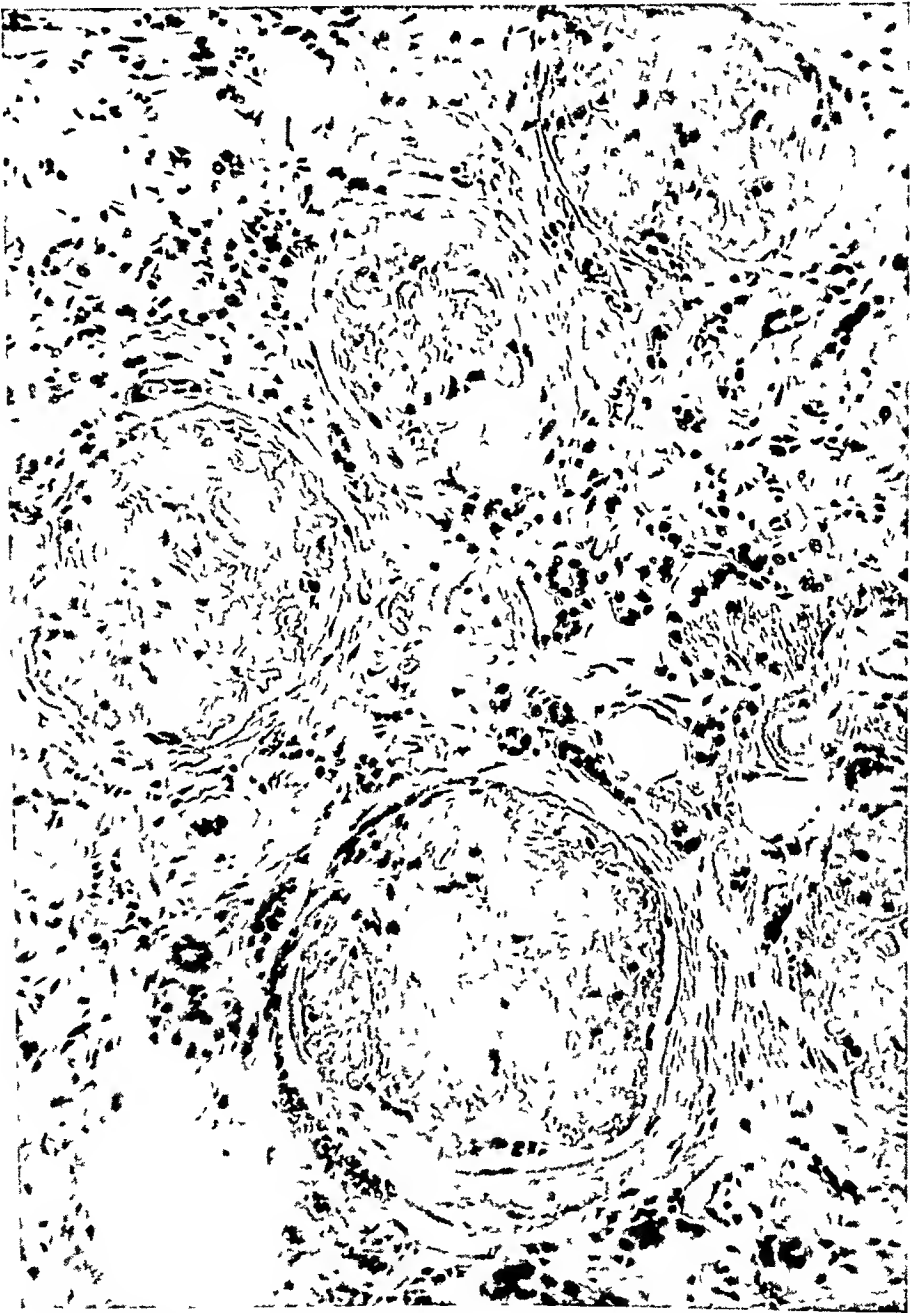


FIG 4 Microphotograph. The glomeruli are almost occluded by amyloid. The tubules are atrophic and frequently have marked deposits of amyloid.

The pericardium appears acutely inflamed. There is a fibrinous exudate on the surface, and the membranes are infiltrated with polymorphonuclear neutrophils. The small blood vessels of the liver and spleen appear slightly thickened. The

media contains a slight amount of amyloid. The hepatic parenchyma is slightly fatty but otherwise shows no evidence of disease. The malpighian corpuscles of the spleen occasionally contain a slight deposit of amyloid.

The renal glomeruli are occasionally normal in size, but usually they are small and contracted. Each glomerulus appears to be filled with amyloid. Few capillaries containing blood are demonstrable. The remnants of the tubules appear as thin tubes of amyloid with casts and some desquamated epithelium in the lumina. (Figure 4)

DISCUSSION

This case represents one in which the amyloid disease is almost wholly confined to the kidneys. It is unusual, for that reason, and also for the fact that it did not have the usual provocative causes so often associated with amyloid disease. It is true that the patient had pulmonary tuberculosis and was confined to the Sanatorium for two and one-half years (1921-1924). Yet, from 1924 until the time of his death, he was examined from two to four times a year, both by physical and roentgen examination, and there was no evidence of activation of his pulmonary tuberculosis. The first sign of amyloid disease appeared during this period of inactivity of his tuberculosis (1927). He did have suppuration of the right cervical glands two years prior to death. This lasted only four months and was considered tuberculous even though this could not be proved either by direct smear or guinea pig inoculation. But since this suppuration did not appear until five years after his first urinary findings, it cannot therefore be considered a predisposing factor.

The limitation of the amyloidosis to the kidneys is quite uncommon. In Bell's series of 65 cases, only two had the amyloid confined to these organs. Raubitschek found only two cases in a series of 72, in which the liver and spleen were not involved. In our own series of 109 cases, the kidneys were the almost exclusive sites of deposit in only this one instance. Since the publication of Bell's paper in 1933, amyloidosis involving the kidneys alone has been reported by Rosenblatt (2) and Perla and Gross (2).

In every instance in Bell's series of 33 cases with tuberculosis, there was extensive chronic suppuration. In our case the suppuration was present in the form of minute cavities, but these were so small that it seems unlikely they would cause the changes which led to death. They could not be seen on roentgen examination. The pulmonary tuberculosis was certainly inactive until the terminal stages. The cavities gave no symptoms whatever, and each of the three cavities was only 7 mm in diameter.

Death from amyloid disease by uremia, although quite rare, is probably more common than is generally supposed. Perla and Gross go so far as to state that "Uremia complicating amyloidosis of the kidney has been observed not infrequently." Bell found only 10 cases reported before 1933, and since that time there are only nine reported by the following: Dixon (1), Perla and Gross (2), Carey (1), Willer (2), Fahr (1), Langeion et al (1), and Mahoudeau et al (1).

The roentgen picture of the kidney is unique. We have been unable to find another case in which the pelves were so deformed as to give the appearance of large kidneys. Moreover, the presence of large and a somewhat irregular mass detectable on casual palpation seemed to lend confirmation to the diagnosis of polycystic kidney. The presence of a mass in the right upper quad-

rant can be accounted for by the low position of the right kidney, but the apparent decrease in size still lacks a satisfactory explanation

SUMMARY

1 At the time of onset of the renal amyloidosis, the patient had arrested pulmonary tuberculosis with no extra-pulmonary complications. His early history, however, revealed two conditions found in association with amyloid, namely, adenitis and enteritis.

2 The patient's intake and output over a period of observation, illustrates a paradoxical diuretic response to the forcing and probably to the limitation of fluid intake, and the diuretic effect of concentrated dextrose given by vein and skimmed milk administered according to Karell procedure in urinary suppression.

3 The presence of a mass in the right upper quadrant and the roentgen findings of the renal pelvis led to an erroneous diagnosis of bilateral polycystic kidney.

4 The patient died in uremia due to renal amyloidosis.

5 Unusual also was the recovery from non-contagious parotitis and the unexpected response to the administration of iron in the marked anemia accompanying renal insufficiency.

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EDITORIAL

VIRUS TUMORS

The volume and the highly specialized character of investigative work on the nature of malignant growths has to some extent rendered this field of medicine an obscure one for physicians. Certain recent advances in our knowledge of tumor producing agents may well have escaped general recognition.

In the early years of this century the possibility of the transmission of certain spontaneous new growths of animals to others of the same species by inoculation of bits of tumor tissue gained acceptance. Jensen in 1902 through his careful studies of the transmission of a spontaneous carcinoma of a white mouse helped greatly clearly to define the conditions necessary for the success of such inoculations. In the course of his investigations, he studied the behavior of the fragment of implanted growth. It was his purpose to determine whether the tumor that resulted arose from the tumor cells that had been injected, or from the cells of the host's tissues. By histological study of different stages, he concluded that whereas the central portion of the implant underwent necrosis, the marginal cells multiplied and formed the new growth. This indicated that these tumors were in a sense tissue cultures *in vivo* and that by repeating transfers, one was carrying on indefinitely the same race of cells. This conclusion of Jensen's accorded well with the studies of the period which had failed to disclose in neoplasms any extracellular infective agent which could be considered causative. It seemed to place the tumor cell itself in the position of being the ultimate carrier of the disease. The search for bacteria, fungi, or protozoa which could cause cancer remained fruitless, and infection as a cause for neoplasms appeared less and less likely.

The nature of irritants which acted as a factor in stimulating neoplastic growth came to be the central problem of cancer research on etiology and, especially since the discovery of coal tar cancer in animals by Yamagiwa and Itchikawa in 1915, this subject of chemical carcinogenic agents has been most intensively investigated.

In 1911, however, the theory of infection as a cause for neoplasms was rejuvenated by the publication of Peyton Rous' discovery of a chicken tumor which could be transmitted by a cell free filtrate of the tumor tissue. The widespread confirmation of this work and its further extension to certain other tumors of fowls proved conclusively that, in the case of these neoplasms at least, some other agent than the living tumor cell could transmit the neoplasm to closely related animals of the same species. Moreover, the growths incited in the host's tissues by the injection of the tumor filtrate were sufficiently similar to indicate a tissue specificity of the tumor-producing effect.

The nature of the agent in the tumor filtrate is still unknown in spite of intensive study of the problem. Many of its attributes, however, have been determined. It is invisible, it is filtrable, it is about 100 M μ in size, it is dependent for increase upon association with living cells, it induces the formation of neutralizing antibodies which act upon it *in vitro* but from which it is protected *in vivo* by its association with cells, it causes morbid changes in cells and induces proliferation to cause neoplasms. The growth of knowledge concerning virus diseases has shown that such are the attributes of certain types of viruses. As Rous has recently succinctly stated: "A comparison makes plain that the agents must be termed viruses or else that the criteria must be rejected whereby the latter are now recognized as such."

The classification of the agent as a virus does not of course settle the matter as to whether it is to be considered as living matter or an inanimate stimulus. This fundamental question is still an open one for all the viruses.

More vital is it to know how large a part viruses, whatever their ultimate nature, may play in the genesis of tumors. For many years their importance seemed relatively circumscribed, since no virus tumor of mammals had been observed. However, recently a virus-induced papilloma of wild rabbits has been described by Shope and intensively studied by Rous and others. A filtrate of this tumor was found to cause abundant warty growth when rubbed on the abraded skin of the domestic rabbit. In this animal the growth did not always retain the characteristics of a benign papilloma but instead developed typical cancerous growths with not infrequent metastases to regional glands and to the lungs. The virus can not be demonstrated in extracts of these cancers. The question therefore arises whether the cancerous transformation is due to the virus or to some further cause acting upon the virus induced papilloma. Rous notes, however, that in certain instances he has transferred cancer tissue from a metastasis of the original growth to the tissues of another rabbit and that with the growth of this implant this second animal developed in its blood neutralizing antibodies for the original virus. This speaks at least for the continued presence of the virus in the malignant stage of the growth.

The production of cancerous growths in a mammal by means of a virus will stimulate even greater interest in this type of carcinogenesis. The determination of the ultimate significance of viruses in the etiology of cancer must await, however, the results of many future investigations.

REVIEWS

Eugenical Sterilization By The Committee of the American Neurological Association for the Investigation of Eugenical Sterilization 211 pages, 22 × 15 cm The Macmillan Company, New York City 1936 Price, \$3 00

This book is the published report of a special committee of the American Neurological Society. The report first presents a brief history of legal sterilization and then a summary of the existing laws in the United States and in foreign countries. A critical review follows of the main arguments for sterilization, the reputed increase of insanity and defective mentality, the reputed increased propagation rate of the mentally diseased or defective, and the inheritability of mental diseases. The available data are shown to render questionable the validity of these assumptions unless in greatly qualified form. The Committee felt it could only recommend sterilization in selected cases of certain diseases and then only with the consent of the patient or those responsible for him. This book is a valuable corrective to much loose thinking and writing on this subject.

M C P

Failure of the Circulation By TINSLEY RANDOLPH HARRISON, M D 396 pages, 23 × 15½ cm The Williams & Wilkins Company, Baltimore Maryland 1935 Price, \$4 50

Students of the pathologic physiology of the circulation have followed with interest the investigations of Dr. Harrison and his colleagues at Vanderbilt University. In this volume a point of view attained by this group as to the meaning and mechanism of congestive heart failure is ably presented. No attempt is made to minimize the uncertainty still prevailing as to the nature of certain phenomena but from the existing data a strong argument is drawn that backward failure, or back pressure from the left and the right ventricles is the source of the congestive process. Diminished cardiac output is shown to be often present in conditions unaccompanied by evidence of congestive failure and to be often absent in typical instances of congestive failure. Hence it is argued "forward failure," or diminished output, cannot explain congestive failure. The discussion of the significance of cardiac dilatation and hypertrophy is of particular interest.

The sections dealing with failure of the "shock" type and failure through coronary disease seem much less adequate than the main section of the book. The inclusion under coronary disease of purely clinical description and of therapeutic recommendations does not seem in keeping with the purpose of the volume.

The frank espousal of a theory is much more stimulating than the mere presentation of a mass of data. The book should interest every thoughtful clinician.

M C P

An Index of Treatment By various writers, edited by ROBERT HUTCHINSON, M D, LL D, F R C P Eleventh Edition, Revised Super Roy 8 10 1020 pages, 18 × 26 cm Wm. Wood and Co., Baltimore 1936 Price, \$12 00

This work is a companion volume accompanying texts on Symptomatology, Diagnosis, and Prognosis. It attempts to cover within the space of a thousand pages the therapy of practically every medical and surgical condition on record. Obviously such discussion must be brief.

To the reviewer it seems neither wise nor practical to present the operative therapy of acute appendicitis, together with the management of its complications.

and after-treatment, within the space of two pages. In the hands of one in need of such information, it might be more dangerous than helpful. The same comment might be offered concerning many of the operative procedures described—none of which should be attempted without a background of surgical experience which would render such discussion unnecessary.

While the medical topics discussed are not subject to the above criticisms, they are of necessity brief. Many methods are mentioned which may rightly be considered outmoded—the use of leeches, for example, as recommended for relief of pleuritic pain in pneumonia, and precordial pain in acute rheumatic carditis. The section on poisons might be of convenience for ready reference. The discussion of hypnotism would seem of little value to the average reader of the volume. The method of antiluetic therapy advised is not adequate according to the standards established in this country, and adherence to it might give rise to dangerous end-results.

In our opinion this volume cannot be said to fulfill satisfactorily the implications of its title.

G W B

COLLEGE NEWS NOTES

NOMINATIONS, 1937-38

Elective Offices

Dr James H Means, President-Elect, Boston, Mass, accedes to the Presidency

New Nominations

President-Elect	William J Kerr, San Francisco, Calif
First Vice-President	David P Barr, St Louis, Mo
Second Vice-President	G Gill Richards, Salt Lake City, Utah
Third Vice-President	William Gerry Morgan, Washington, D C

Respectfully submitted,

Committee on Nominations,

WILLIAM B BREED

JAMES D BRUCE

CHARLES T STONT

CHARLES F MARTIN

GEORGE MORRIS PIERSOL, *Chairman*

GIFTS TO THE COLLEGE LIBRARY

Acknowledgment is made of the receipt of the following gifts by the authors to the College Library of publications by members

Books

Dr Howard T Karsner (Fellow), Cleveland, Ohio—one autographed book, "Human Pathology," Fourth Edition,
Dr W McKim Marriott (Fellow—Deceased), San Francisco—one book, "Infant Nutrition",
Dr F M Pottenger (Fellow), Monrovia, Calif—one autographed book, "Tuberculosis in the Child and the Adult",
Dr Paul D White (Fellow), Boston, Mass—One autographed book, "Heart Disease," Second Edition,
Dr Clarence J Tidmarsh (Associate), Montreal, Que—one book, "Chronic Indigestion"

Reprints

Dr William E Ash (Fellow), Council Bluffs, Iowa—1 reprint,
Dr John L Goforth (Fellow), Dallas, Tex—1 reprint,
Dr William A Groat (Fellow), Syracuse, N Y—1 reprint,
Dr Manfred Kraemer (Fellow), Newark N J—1 reprint,
Dr D O N Lindberg (Fellow), Decatur, Ill—1 reprint,
Dr Harry R Litchfield, Brooklyn, N Y—1 reprint,
Dr Fred M Meixner (Fellow), Peoria, Ill—1 reprint,
Dr George R Minot (Fellow), Boston, Mass—2 reprints,
Dr Edgar A Hines, Jr (Associate), Rochester, Minn—4 reprints,
Dr Maurice S Jacobs (Associate), Philadelphia, Pa—5 reprints,
Dr Leslie M Smith (Associate), El Paso, Texas—3 reprints

We also gratefully acknowledge the gift of the following books to the College Library by the author, Dr Charles Solomon, Brooklyn "Pharmacology, Materia Medica and Therapeutics", "Prescription Writing and Formulary"

NEW LIFE MEMBERS

The following have become Life Members of the American College of Physicians at the dates indicated, making a total of seventy-seven Life Members

Dr Samuel A Vogel, Buffalo, N Y, January 25, 1937,
 Dr Mills Sturtevant, New York, N Y, February 4, 1937,
 Dr Russell M Wilder, Rochester, Minn, February 5, 1937

ANNUAL MEETING OF THE NEBRASKA MEMBERS OF THE COLLEGE

The Nebraska College Meeting was held January 13, Lincoln, Nebraska, Hotel Cornhusker

A scientific program was held during the afternoon, which was followed by a banquet at 6 00 pm A short business session followed the dinner and then the scientific program was continued It was a very enthusiastic meeting and it was decided that the next meeting would be held in Omaha

Afternoon Program Dr J C Thompson (Fellow), "Desiccated Duodenal Mucosa in the Treatment of Anemia", Dr J Marshall Neely (Fellow), "The Pathogenesis of Tuberculous Meningitis", Dr H E Flansburg (Fellow), "Report of an Atypical Case of Pulmonary Congestion Due to Congestive Failure", Dr H J Lehnhoff, "Report on Cases of Simon's Disease", Dr F L Rogers (Fellow) and Dr G W Covey (Fellow), "Report of a Case of Thymoma with Cardiac Metastasis", Dr Edward Meister, "Report of Case of Coarctation of the Aorta" Dr E H Hashinger (Associate), Kansas City, Mo, was the guest speaker of the evening and discussed "The Practical Side of Endocrine Therapy"

ADOLPH SACHS, M D, F A C P,
 Governor for Nebraska

MEETING OF THE AMERICAN BOARD OF INTERNAL MEDICINE

The Chairman of the American Board of Internal Medicine, Dr Walter L Biering, has reported a meeting of the Board at Chicago, February 13, 14 and 15, 1937 A report on the candidates who took the Board's written examination, December 14, 1936, reveals that forty-eight candidates were passed and eight were recommended to repeat the examination in October, 1937 The next written examination is scheduled for March 22, 1937 The first practical or clinical examination will be conducted on Friday, April 23, at the City Hospital, St Louis, Mo, beginning at 9 00 a m, this being the closing day of the Twenty-First Annual Session of the American College of Physicians at St Louis The second practical examination will be conducted by members of the Board on Saturday, June 5, 1937, in Philadelphia

ANNUAL CONGRESS ON MEDICAL EDUCATION AND LICENSURE

The Thirty-Third Annual Congress on Medical Education and Licensure was held in Chicago, February 15 to 16, 1937 Among Fellows of the College who participated are the following

Dr William D Cutter, Chicago, Ill, "Report of the Survey to Individual Schools",
 Dr R L Sensenich, South Bend, Ind, "The Doctor and the Narcotic Violator",

- Dr Torald Sollmann, Cleveland, Ohio, "The Why, What and How of the Medical Scholastic Aptitude Test",
Dr Howard T Karsner, Cleveland, Ohio, "Philosophical Comments on Examinations",
Dr Harold Rypins, Albany, N Y, "Increase in the Number of Practitioners in the Country",
Dr Joseph C Doane, Philadelphia, Pa, "How Nursing May Promote Inter-Professional Relationships"
-

Dr F H Voss (Fellow), Kingston, N Y, has been elected President of the Ulster County Medical Society for 1937 Dr Voss also has been appointed by the Mayor as a member of the Board of Managers of the Kingston City Laboratory for a period of three years

Dr William C Voorsanger (Fellow), San Francisco, delivered the third Lane Popular Medical Lecture February 5, 1937, under the auspices of the Stanford University School of Medicine, his subject being "Recent Advances in the Treatment of Tuberculosis"

Dr L D Sargent (Fellow), Washington, Pa, has been elected a Trustee of the Pennsylvania State Medical Society and Councilor of the Eleventh District

Dr Fred M Meixner (Fellow), Peoria, Ill, has been reelected President of the Peoria County Tuberculosis Association Dr Meixner is a Director of the Illinois State Tuberculosis Association and also a member of a special committee, of which Dr Maxim Pollock (Fellow), Peoria, is chairman, to plan a tuberculosis survey in the schools of the City of Peoria

Dr John C Ruddock (Fellow) and Dr Howard F West (Fellow), both of Los Angeles, have been made President and Secretary-Treasurer, respectively, of the newly organized California Heart Association

The First New Orleans Graduate Medical Assembly was held March 8-11, with a program of clinical demonstrations, didactic lectures, round table discussions and symposia Among Fellows of the College outside of New Orleans who contributed to the program were Dr Anthony Bassler, New York City, Dr Russell Cecil, New York City, Dr John A Kolmer, Philadelphia, Dr Julius H Hess, Chicago, and Dr George Morris Piersol, Philadelphia

Dr Louis P Hamburger (Fellow), Associate in Medicine, Johns Hopkins University School of Medicine, has been appointed consultant to the Baltimore City Health Department

Dr Thomas Hodge McGavack (Associate), formerly of San Francisco, has been appointed Associate Professor of Medicine at the New York Medical College and Flower Hospital

Dr J Arthur Myers (Fellow), Minneapolis, addressed the forty-fifth annual meeting of the Pennsylvania Tuberculosis Society in Philadelphia on January 20

Dr J Burns Amberson, Jr (Fellow), has been promoted to Professor of Clinical Medicine on the Faculty of New York University College of Medicine

Dr Elmer L Sevringhaus (Fellow), Madison, Wis, and Dr Francis E Senear (Fellow), Chicago, were among those who appeared on the program of the ninth spring clinical conference of the Dallas Southern Clinical Society, March 15 to 18

A Pneumonia Commission has been appointed by the President of the Medical Society of Virginia, Dr J Morrison Hutcheson (Fellow), Richmond, to investigate the incidence and types of the disease in Virginia and the kind of management in vogue. Members of the Commission include Dr Wyndham B Blanton (Fellow), Richmond, chairman, Dr Walter B Martin (Fellow), Norfolk, Dr Henry B Mulholland (Fellow), Charlottesville, Dr Philip S Smith (Fellow), Abingdon, and Dr Harry Walker (Associate), Richmond

Dr Milton M Portis (Fellow), Chicago, is a member of the professional committee for medicine in the Illinois State Department of Registration and Education

Dr James H Means (Fellow and President-Elect), Boston, addressed the North Side Branch of the Chicago Medical Society, February 4, on "The Rôle of the Physician in the Management of the Patient with Thyrotoxicosis"

Honorary fellowship in the Royal College of Physicians and Surgeons (Canada) was recently conferred upon Dr Henry A Christian (Fellow), Boston, Mass

Dr Cyrus C Sturgis (Fellow), Ann Arbor, Mich, Dr Andrew C Ivy (Fellow), Chicago, and Dr Jonathan C Meakins (Fellow), Montreal, were among the guest speakers at the fifty-third annual meeting of the Mid-South Post Graduate Medical Assembly, held at Memphis, Tenn, February 16 to 19

Dr Carl J Wiggers (Fellow), Professor of Physiology, Western Reserve University School of Medicine, Cleveland, Ohio, is on sabbatical leave, while on a trip around the world

The Medical Society of the State of Pennsylvania has established a commission for the study of pneumonia control. Among the members of the commission are Drs Edward L Bortz (Fellow), Philadelphia, chairman, Edward W Bixby (Associate), Wilkes-Barre, George J Kastlin (Fellow) and Clifford C Hartman (Fellow), Pittsburgh, T Grier Miller (Fellow), Henry K Mohler (Fellow) and Leon H Collins, Jr (Associate), Philadelphia

Dr Thomas Klein (Fellow) has been appointed Professor of Clinical Medicine at Temple University School of Medicine, Philadelphia

Dr Samuel B Hadden (Fellow) has been promoted to Clinical Professor of Neurology at Temple University School of Medicine, Philadelphia

Dr Thomas Parran (Fellow), Surgeon General of the U S Public Health Service, was one of the principal speakers at the laying of the cornerstone of the U S Narcotic Farm at Fort Worth, Texas, February 13. This is the second narcotic farm to be built by the U S Public Health Service under the jurisdiction of the division of mental hygiene. The first was opened during May, 1935, at Lexington, Ky, where 1,240 patients were admitted during the first year of operation. The annual report of the Public Health Service states "There is no question that the treatment of narcotic addiction in a hospital has distinct advantages over the management of such cases in a correctional institution."

Dr Fred E Clow (Fellow), Wolfeboro, N H, was elected Secretary-Treasurer of the State Board of Registration in Medicine

Dr Josiah N Hall (Fellow), Emeritus Professor of Medicine, University of Colorado School of Medicine, Denver, and a former Governor of the College for Colorado, was the guest of honor at a testimonial dinner, February 20, given by Dr Hubert Work (Fellow), formerly Secretary of the Interior Dr Hall has retired from active practice as of March 1 He is seventy-seven years of age, a native of Chelsea, Mass, and a graduate of Harvard University Medical School, 1882 His medical career has been rich in experience and service He has contributed much, has sown well, his harvest is one of many honors, of love and of appreciation Tribute was paid him in 1936 by the Colorado State Medical Society when the banquet and president's reception were dedicated to him in recognition of his fiftieth year of attendance at the annual sessions of that Society

Dr George W McCoy (Fellow), who since 1915 has been director of the National Institute of Health, formerly known as the "Hygienic Laboratory," has been relieved of this appointment to make investigations on leprosy Dr McCoy is a native of Cumberland Valley, Pa, is sixty years of age and a graduate of the University of Pennsylvania School of Medicine, 1898 He entered the Public Health and Marine Hospital Service in 1905 as assistant surgeon, in 1913 he became surgeon in the U S Public Health Service He was named medical director July 1, 1930 From 1908 to 1911 he was in charge of the U S Plague Laboratory, San Francisco, and from 1911 to 1915 director of the U S Leprosy Station, concurrently serving during this period as sanitary adviser to the Hawaiian Government He has written numerous papers on public health and bacteriological subjects He was President of the Washington Academy of Sciences during 1935

Dr Thomas Parran (Fellow), Surgeon General of the U S Public Health Service, Washington, received the honorary degree of Doctor of Pharmacy at the 116th annual celebration of Founders' Day at the Philadelphia College of Pharmacy and Science on February 23 Dr Parran delivered an address, "The Aims and Ideals of the United States Public Health Service"

ERRATUM

In the College News Notes of the January 1937 issue, page 1071, of the Annals of Internal Medicine, announcement was made that Dr Elliott P Joslin of Boston is President of the Interstate Post-Graduate Medical Association Dr Joslin is President-Elect at the present time, Dr John F Erdmann of New York City is President

OBITUARIES

DR LUTHER FISKE WARREN

Dr Luther Fiske Warren was born in Waterford, Michigan, September 20, 1885, the son of Charles B Warren and Anna Weinmann. He died on January 18, 1937, at his home, 81 Pierrepont Street, Brooklyn, after a long period of intense suffering, of generalized metastases resulting from a mammary gland carcinoma removed several years previously. He is survived by his widow, his mother, his two sons, Dr Charles Ford and Dr Robert Fiske, both connected with the Long Island College Hospital, a daughter, Miss Edith Warren, and a brother and sister.

From earliest childhood Dr Warren began to exhibit his enormous capacity for work. As a small child he worked on the farm, while attending the local school. Going to Ann Arbor in order to complete the last two years of high school there, he began to shift for himself, working his way successively through the literary and medical schools of the University of Michigan. As a Freshman in the literary school he married Miss Agnes Chubb, a student in the dental school, and before he had finished his medical course his wife had borne him two children, and had had an operation for gall-stones. In spite of the cares connected with providing for this family, in his junior year in medical school he was elected to the honorary fraternity, Alpha Omega Alpha, and in his senior year to Sigma Xi. He received the degree of A B in 1907 and M D in 1909. Following his graduation from medical school he was kept on as Instructor in Medicine, teaching physical diagnosis and giving the first course in clinical microscopy ever given at the School. As a result, even though so young, he was frequently called in consultation by older physicians in Ann Arbor. During the three years of this work his daughter was born.

In 1912 Dr Warren was called to the Long Island College Hospital, Brooklyn, to be director of the newly established clinical laboratories, with the title of Assistant Professor of Clinical Medicine. His prodigious energy and remarkable teaching ability resulted in rapid promotion. From 1915 to 1917 he was Associate Professor of Medicine, from 1917-1919, Acting Professor of Medicine, and in 1919 was made Professor of Medicine. With the reorganization of the College in 1930, he became Professor of Medicine of the Long Island College of Medicine, a post he was holding at his death. He also held many other medical appointments in Brooklyn, being Physician-in-Chief at the Long Island College Hospital and St Johns Hospital, Medical Director of the Brooklyn Home for Consumptives, which he completely reorganized after his appointment in 1931, and Consulting Physician to the Methodist Episcopal, Coney Island, Harbor, Lutheran, Southside and Brunswick General Hospitals.



DR LUTHER F WARREN
REGENT OF THE AMERICAN COLLEGE OF PHYSICIANS

Dr Warren's medical society memberships were very extensive and he held many official positions in them. A Fellow of the American College of Physicians since 1919, he was Governor from 1931 to 1933 and a Regent from 1933 until his death. He served on many committees, giving most of his time and service to the Committee on Credentials. He was an advisor to the American Board of Internal Medicine. Memberships in national societies included the American Medical Association, American Heart Association, National Tuberculosis Association, Association for Study of Internal Secretions, American Society of Tropical Medicine, American Society for the Advancement of Science. Local societies included the New York Academy of Medicine, Medical Society of the County of Kings (President, 1930), Brooklyn Society of Internal Medicine, Brooklyn Pathological Society, Brooklyn Medical Association and Associated Physicians of Long Island. He was Chairman of the Public Relations Committee of the Medical Society of the State of New York. In addition to the enormous amount of time spent in teaching, in administration of his departments in the medical school and hospital and in his medical society activities, Dr Warren was an examiner in diagnosis of the New York State Board of Medical Examiners from 1933 until his death, and was an active participant in the activities of many civic and educational organizations. He was a member of the Board of Trustees of Polytechnic Institute and of the Packer Collegiate Institute, a member of the Board of Directors of the Brooklyn Chamber of Commerce and Chairman of its Public Health Committee, President of the Brooklyn Health Council and Member of Board of Directors of the Brooklyn Council for Social Planning.

From 1911 onward Dr Warren began to contribute to medical literature, his early works being devoted to clinical laboratory methods. He contributed a Section on Diseases of the Bronchi to Tice's Practice of Medicine and was Medical Editor of the International Medical Digest from 1920 to 1928. He was frequently called upon to speak or to discuss papers at medical meetings and always gave freely of his knowledge.

On reading of the foregoing list of activities of this remarkable man, one would conclude that here was a full-time professor in the medical school, with nothing to do but to teach, to administer his departments and to attend meetings. But this was decidedly not the case with Dr Warren. His private practice was one of the largest in Brooklyn, and no one was called upon more for consultation work. He was worshiped by his students, and when they entered practice they constantly sought his help in difficult cases. He reported at the hospital at 8:30 every morning, worked all day and evening, and would often say that his only time for study and for preparation for his day's work would be between 12:00 and 3:00 a.m. Although slight of build he was a man of iron. His muscles were like whip-cords. He gloried in his farm at Brewster, New York, where he experimented with



DR FRANK SMITHIES
MASTER OF THE AMERICAN COLLEGE OF PHYSICIANS

intensive production of crops and animals. He was a loving husband and father, taking particular delight in recounting the events of his children's educational and developmental life. He and Mrs. Warren were genial hosts and entered much into the social activities of Brooklyn. His daughter's debut was an event of importance in the city's social life.

Those associated with Dr. Warren in his many activities knew him as a man with high ideals, whose large brown eyes would glow and whose firm jaw would set with determination when he was advocating a measure which he considered to be right, or opposing one which he felt would be inadvisable or unjust. He not only worked hard himself, but had the faculty of making others exert themselves to the utmost, so that he lived constantly in an atmosphere of intense activity. It is no wonder that his life should have been ended so soon. He compressed a maximum of living into his 51 years of life.

A. F. R. ANDRESEN, M.D., F.A.C.P.

DR. FRANK SMITHIES

Dr. Frank Smithies (Master) passed away Tuesday morning, February 9, 1937, following a cerebral hemorrhage.

He was born in Elland, England, December 21, 1880, and came to the United States when a very young child and had his elementary school education in Philadelphia and Chicago. He was a graduate of the Calumet High School of Chicago and studied medicine at the University of Michigan, from which school he was graduated in 1904. Following this he went abroad and studied at the University of Berlin and Guy's Hospital, London.

After returning to this country he taught at the Rush Medical College 1904-05, and then at the University of Michigan, 1906-10. He then went to the Mayo Clinic, Rochester, Minn., where he was gastro-enterologist from 1911-14. After this he removed to Chicago, where he practiced diagnostic medicine with especial reference to diseases of the digestive system. From 1915 to 1925 he was professor of medicine at the University of Illinois. He was Attending Physician, Henrotin Hospital, since 1921, Chief of Clinic in Digestive Diseases, Municipal Tuberculosis Sanitarium, Chicago, 1927-30, Consulting Physician of the C. M. & St. P. R. R.

He made many contributions to the medical literature. His papers numbered well over one hundred, including his book on Cancer of the Stomach, published in 1916. He was Editor-in-Chief of the *American Journal of Digestive Diseases and Nutrition*, and Associate Editor of the *American Journal of Syphilis* (St. Louis) and *American Journal of Tropical Medicine* (Baltimore). He was the first Editor of the *Annals of Clinical Medicine*, official journal of the American College of Physicians.

He was past president of the following societies American College of Physicians, 1927-28, American Gastro-Enterological Association, 1929-30, American Society of Tropical Medicine, 1931-32, American Therapeutic Society, 1932-33

His hobbies were reading and fishing He collected many rare books and was particularly interested in books on arctic explorations of which he had an unusually large collection

In 1917 he was made a Fellow of the American College of Physicians, and elected a member of its Council later in the same year In 1918, together with a group of prominent Internists throughout the country, the reorganization of the American College of Physicians was undertaken, with Dr Smithies as Secretary General The rapid advancement of the College from that time on was recognized as due, to a large extent, to the forceful presentation by Dr Smithies of the great need for the organization by the Internists of America He introduced the clinical character of its annual meetings, stimulating great interest in these gatherings In recognition of service to the College, he was made one of the six Masters of the society, he being the fourth of these to pass away He was liaison representative of French and American Medicine in this Country, and was made a Chevalier of the Legion of Honor of France

A great soul has gone from us Frank Smithies is no longer with us In our hearts and minds we realize that we have sustained a major loss, the magnitude of which grows as we contemplate his achievements, his capacity of analytical ingenuity, his editorial versatility, his differential judgment, an outstanding gift of sympathetic understanding as well as a prophetic vision of the future of Internal Medicine His virile spirit enabled him to surmount difficulties which would have halted less courageous souls

CLEMENT R JONES, M D , F A C P

DR LOUIS HENRY FALES

Dr Louis Henry Fales (Fellow), Livermore, Calif, died February 13, 1937, at Fort Miley, San Francisco, of anemia

Dr Fales was born at Janesville, Wis, October 7, 1871 He received the degree of Bachelor of Laws from the University of Wisconsin in 1893 and the degree of Doctor of Medicine from Rush Medical College, Chicago, in 1897 He interned at St Luke's Hospital, Chicago, 1897-99 He was Physician-in-Charge of the Bilibid Prison Hospital, Manila, P I, 1901-03, Physician-in-Charge, Baguia Sanitarium, Baguia, P I, 1903-04, in 1918 he was commissioned Captain in the Medical Corps of the U S Army, and was discharged in 1920 He also held a commission as past assistant surgeon in the U S Public Health Service and assigned to active duty in 1920

He was commissioned surgeon in this Service in 1920. In 1924 he transferred to the U S Veterans Bureau. He served as ward surgeon and acting clinical director of the Veterans Administration Hospital at Palo Alto, Calif, 1924-25, and as ward surgeon, acting clinical director, medical officer in temporary charge and acting roentgenologist at the Veterans Administration Hospital, Livermore, Calif, between 1925 and the date of his death. In his earlier work in the Philippine Islands he was a medical inspector with the Philippine Health and Sanitary Service, and had considerable experience with bubonic plague and cholera at that time.

Dr Fales was the author of a number of articles, appearing in leading medical journals. He was a past president of the Veterans Administration Facility Medical Society, a member of the Alameda County (Calif) Medical Society and a member of the American Tuberculosis Association. In the course of his work he pursued various postgraduate courses at the University of Wisconsin, the U S Army Medical School and the University of California Medical School, always seeking to keep himself well informed of medical progress. He had been a Fellow of the American College of Physicians since 1933.

DR WALTER OLIN NISBET

Walter Olin Nisbet, B S, M D, F A C P, died suddenly in Charlotte, North Carolina, his home, January 18, 1937.

He was born in Lancaster County, South Carolina, October 5, 1866, the son of Dr John Newton and Mary Jane Phifer Nisbet. He graduated at the University of South Carolina in 1885 with the B S degree, receiving his medical degree in 1889 from the Medical College of South Carolina in Charleston, serving his internship in the Roper Hospital in that city. He was a member of the S A E and O D K fraternities.

After ten years of general practice in Richburg, South Carolina, and Waxhaw, North Carolina, he spent a year in study in Berlin, preparatory to entering the field of gastroenterology, in which field he became recognized as one of the leading specialists of the South. He located in Charlotte, North Carolina, at this time, and was dean at the medical school there from 1912 to 1916. With others, he organized the Charlotte Sanatorium in 1909, and continued as a member of its staff as well as that of the Presbyterian Hospital until his retirement in 1934, two years after suffering a coronary occlusion.

Dr Nisbet was for twenty-five years an elder of the Second Presbyterian Church, and was a member of the Charlotte Country Club, his chief interest in sport being in hunting and golf. He was a member of his County and State Medical Societies, the Tri-State Medical Society, the Southern Medical

Association, the American Medical Association, and the Gorgas Memorial Institute of Tropical Medicine, and he became a Fellow of the American College of Physicians in 1923

His contributions in his chosen field were always well informed, illuminating, and authoritative. Ever alert to progress in his chosen line, he was particularly interested in the development and progress of his younger colleagues, all of whom as well as a host of friends throughout the South revere his memory. To them he was ever a source of comfort, strength, and friendly encouragement.

He is survived by his widow, the former Miss Eugenia Heath of Waxhaw, and three sons, Everett, Walter O. Jr., and Dr. Douglas Heath Nisbet, F.A.C.P., who was associated with him in practice for the past eighteen years.

CHARLES H. COCKE, M.D., F.A.C.P.,
Governor for North Carolina

DR. WILLIAM G. STEARNS

William Guilford Stearns was born at Lomax, Wisconsin, February 11, 1865.

He attended Northwestern University Medical School from which he was graduated in 1893. The following year he served an internship at St. Luke's Hospital in Chicago, and the next year acted as Assistant Physician at the Illinois State Hospital for the Insane at Kankakee, Illinois, he served for two years in the same institution as Pathologist and later was the Medical Superintendent for two years. He was Medical Superintendent of the Oakwood and Lake Side Sanatoria, Lake Geneva, Wisconsin, from 1900 to 1904, Professor of Pathology, Anatomy, and General Pathology at Northwestern Dental School, 1894 to 1898, and Assistant Professor of Mental Diseases and Medical Jurisprudence at Northwestern University Medical School, 1898 to 1900. Later he served as Lecturer in Neurology at the College of Physicians and Surgeons in Chicago, 1900 to 1902. In 1898 he was Chairman of the Section on Insanity, National Conference of Charities and Correction. He served with the Medical Advisory Board, Number 3E Selective Service, as a consultant in neuro-psychiatry, 1917 to 1919. He was Medical Director of the North Shore Health Resort, Winnetka, Illinois, 1931 to 1936.

Dr. Stearns was a member of Nu Sigma Nu and Alpha Omega Alpha fraternities. His society memberships included American Medico-Psychiatric Association, Central Neuro-Psychiatric Association, Chicago Medical Society, Illinois State Medical Society, Chicago Neurologic Society, Chicago Society for Prevention and Relief of Heart Disease, Fellow of the

American College of Physicians (1917), American Medical Association and Chicago Institute of Medicine

Dr Stearns was recognized as a member of the profession, highly regarded by his fellow practitioners. His friends in and about Chicago, both professional and others, were legion. He was a man of upright character, noted for his fairness, integrity and good judgment and widely known as a gentleman of fine character, and a physician of unusual talents. The profession in Chicago has lost a man who was an exemplar of a type of character which brings to our profession special regard. He will be sorely missed by those who have had the privilege of knowing him personally.

JAMES G. CARR, M.D., F.A.C.P.,
Governor for Northern Illinois

HISTORIC ST LOUIS

LONG ago the site of St. Louis was peopled by the Mound Builders, a prehistoric race which inhabited the Mississippi Valley. Little is known about them, but it is interesting to note that the ancient Toltecs of Mexico had legends that their nation originally lived in and was driven from a country far away to the northeast. In the collections of the Missouri Historical Society are strange relics of a civilization believed to antedate the Indians and to have represented a superior race.

St. Louis is sometimes called the "Mound City," from the many strange mounds discovered on its site. The largest of these was at what is now Mound Street, at the corner of Broadway. Others were in the present Forest Park. Seven miles east of the city is the famous Cahokia, or "Monk's Mound," said to be the greatest in the world. This mammoth of the group is larger than the greatest Egyptian Pyramid, and appears to be much older. It is an earth pyramid 1,080 feet long, 780 feet wide and 104 feet high, spreading its huge bulk over 15 acres of ground, with terraces at various levels.

The origin of these mounds has long been shrouded in mystery. Warren King Moorehead, Curator of the Museum of Phillips Andover Academy, several years ago made a series of careful excavations and for six weeks peered into the mysteries of these great earth piles, obtaining therefrom much scientific data. He found proof that they were deliberately fashioned by man. It is probable that they were once the site of an ancient city whose population ran into the thousands—perhaps 100,000 persons—who lived and toiled and disappeared long before the beginnings of American chronicles.

The founding of the present city must be attributed to a far-sighted French merchant, named Pierre Laclède Liguist, who conceived the idea of establishing a permanent settlement in some favorable location on the Mississippi. Accompanied by young Auguste Chouteau, he explored the river searching for an ideal spot. In December, as the still preserved record relates, "he fixed upon the place, marked with his own hands some trees and said to Chouteau, 'You will come here as soon as navigation opens and will cause this place to be cleared in order to form our settlement after the plan I shall give you,' and to DeNoyon, Commandant at Fort Des Chartres, he enthusiastically stated that he had found a situation where he was going to form a settlement which might become, hereafter, 'one of the finest cities in America—so many advantages were embraced in this site, by its locality and its central position for forming settlements'."

It was on the evening of February 14, 1764, that Chouteau and a band of thirty French pioneers landed on the west bank of the Mississippi River at what is now the foot of Walnut Street in St. Louis. For four long days they had poled and dragged their heavy craft from Fort Chartres, sixty



FIG 1 Old St Louis Cathedral

miles below Weaned by their labors, they slept that night in the boat On the following morning Chouteau led his men across the sandy beach, up to the plateau overlooking the river and pointed out to them the line of trees which he and Laclede had marked Thus began the building of St Louis

Those were pioneer days The entire upper Mississippi Valley was a silent wilderness Here and there, hundreds of miles apart, were roughly stockaded and scantily garrisoned forts and trading posts, constituting the meager outposts of civilization, the sole refuge against Indian attacks Life was a continued struggle for existence

Other expeditions, French and Spanish, soon sought to overshadow the little settlement of St Louis A Spanish Fort was built a short distance to the north Yet so well had Laclede chosen, and so energetically had his followers labored, that these competitive efforts gradually merged with St Louis itself Within three years its colonists had established valuable fur-trading monopolies with the 28 principal Indian nations, including not only those west of the Mississippi, but also east of the river and even as far north as the Great Lakes These the English tried in vain for many years to break

The fur trade was the commercial cornerstone of St Louis' prosperity Every year saw the city's sphere of influence broaden Up the Mississippi and Missouri crept a line of outposts St Louis became the gateway of a stream of migration, the starting point of expeditions in all directions, some military, some scientific, others to establish new communities or to open commercial avenues The greatest of these, the Lewis and Clark expedition, which was responsible for the opening of the Northwest, left St Louis in 1804 The Frenchmen of St Louis paved the way for the American occupation of Louisiana A branch of the Chouteaus started Kansas City Robidoux, of St Louis, established St Joseph One of the Menards founded Galveston A hundred western cities and towns owe their beginning to St Louisans

THE SIGHTS OF ST LOUIS

No visitor to St Louis should be at a loss as to what to do or what to see Members of the medical profession and their wives who visit St Louis in April will enjoy the Art Museum, the Cahokia Mounds, the Confederate Memorial, the Dent House, Forest Park, Grant's Log Cabin, the Jefferson Memorial, the Lindbergh Trophies, the Old Court House, the Mississippi River Front, Shaw's Gardens, St Louis Municipal Airport, the Zoological Gardens and many other attractions

The St Louis Zoo is worthy of special attention Feeding time in the midafternoon is an event of interest and pleasure for young and old The trained chimpanzees, the monkey kindergarten, the performing tigers and the hungry, barking sea lions constitute a show which will long be remembered The collection of reptiles, now housed in a new and beautiful build-

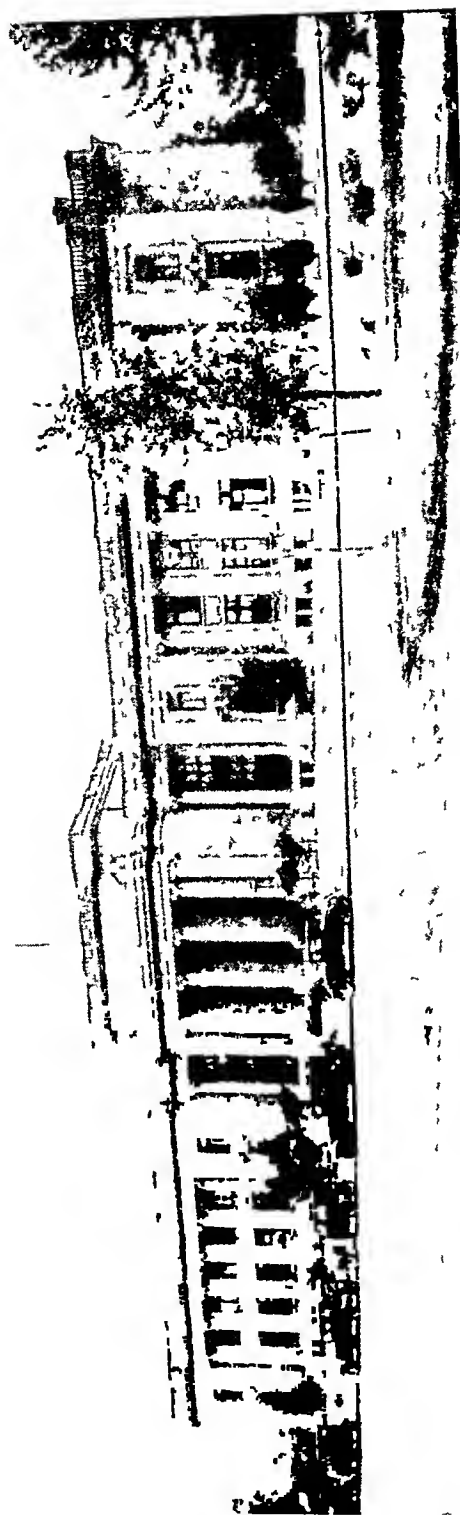


FIG 2 The Jefferson Memorial which houses the Records of the Missouri Historical Society and the Lindbergh trophies

ing, is outstanding. The cageless bear pits, which have attracted the notice of zoological experts from all over the world, are artificial rocky dens with earth filled fissures from which grow native shrubs and evergreens. This unique method of exhibiting wild animals has proved so satisfactory that similar accommodations have been provided for many other creatures in the zoo.

After visiting the Zoological Gardens one should see the Jefferson Memorial, an imposing marble structure which stands on the site of the main entrance of the World's Fair of 1904. Here one can see relics of the Mound Builders, curios of the Indian tribes who traded with the founders of St. Louis, original manuscripts of the French and Spanish days in Missouri, relics of the pioneers and of the Revolutionary, Mexican, Spanish-American and World Wars. In addition to the third largest collection of Jefferson manuscripts, the Jefferson Memorial holds a large part of the original documents of the Hamilton-Burr controversy, which culminated in the death of one brilliant man and the destruction of the career of another. In the display cases many of the manuscript records of the Lewis and Clark Expedition may be seen.

Of supreme interest today is the complete showing of the famous Lindbergh Collection, including gifts, medals, trophies and souvenirs from a score of foreign countries and from thousands of sources. These have been viewed by more than 5,000,000 persons since they were put on exhibit. From 500 to 1200 people call to see these trophies daily. Colonel Lindbergh recently deeded to the Missouri Historical Society custody of the hundreds of mementos which have come to him in connection with the epoch-making flight of the "Spirit of St. Louis" across the Atlantic, and his friendship tour to the countries of Mexico, Central and South America.

St. Louis' Art Museum, erected during the World's Fair of 1904 as a permanent building, stands on the crest of Art Hill in Forest Park, overlooking the West End residential district and the suburbs which stretch out to the north and west. To its immediate foreground is a vista of sloping landscaped lawn, of glimmering lake and of speeding motor-cars on the winding drives beyond. No other museum building in America has a setting of such natural splendor. This great treasure-house of art is open daily, free to all. Ranked as one of the four best art galleries in the United States, the Museum contains rich exhibits of paintings, casts, sculpture, marble, drawings, architecture and applied art. Many rare canvases, the work of the old masters, are here. Its collection of Chinese bronzes, ceramics and paintings is one of the finest of its kind. Visitors will be especially interested in the period rooms and in the remarkable carved outdoor staircase from Morlaix, in Brittany. St. Louis is one of the few cities in the United States which fosters the development of artistic and cultural facilities for the public by a direct tax for the maintenance and development of its Art Museum, thereby making superior advantages of this kind available to everyone.

During a visit to Forest Park one should not miss a glimpse of the famous Jewel Box, a rare and artistic display of flowers and other plants held regularly in the city's greenhouses located in Forest Park. Thousands of persons annually visit the splendid displays arranged there.



FIG 3 Art Museum

Entirely separate from the Jewel Box is the Missouri Botanical Garden. Founded in 1860 by Henry Shaw, a St. Louis philanthropist, it is popularly known as Shaw's Garden, and ranks second only to the famous Kew Gardens of England. It contains the largest collection of plant life in the western hemisphere and is famous the world over for its wealth of botanical species and its beautiful floral displays. It comprises a city garden of about 75 acres, an out-of-town extension of more than 1,625 acres, and a tropical extension at Balboa, Panama.

At the city garden large conservatories are maintained, containing a varied collection of tropical plants and providing for an almost continuous display of chrysanthemums, orchids, lilies, tropical vines, ferns, palms, Australian, Philippine and Japanese plants, desert cacti and other growing plants. Out of doors are to be found representative gardens of roses, irises, water

lies, and collections of every other kind of plant which can be grown in the region of St. Louis. The orchid and chrysanthemum shows have established national reputations for the gorgeousness and rarity of their blooms and for the beauty and method of their display. Altogether, more than 11,000 species of plants from all climes and all parts of the globe are to be seen here.



FIG. 4 The Jewel Box in Forest Park

One of the best botanical libraries in the country, one of the largest herbaria in the United States, laboratories for scientific work and a school for gardening combine the features of a pleasure-ground with the facilities of an institution of research.

The out-of-town garden, which is constantly being developed, is already one of the best localities in the state for the growing of wild flowers and trees. The propagation of rare and delicate plants away from conditions unfavorable to early plant life incident to a city location is carried on there. Besides growing much material for later exhibit in the city garden, there is gradually being developed an adequate arboretum, which in time will probably become the most complete reservation for trees and native flora in the temperate zone.

MEDICAL ST LOUIS

The St Louis Medical Society was founded in 1836 by a small group of physicians and until 1850 was known as the Medical Society of the State of Missouri. At that time the Missouri State Medical Society was organized, and the name of the local organization was changed to the St Louis Medical Society.

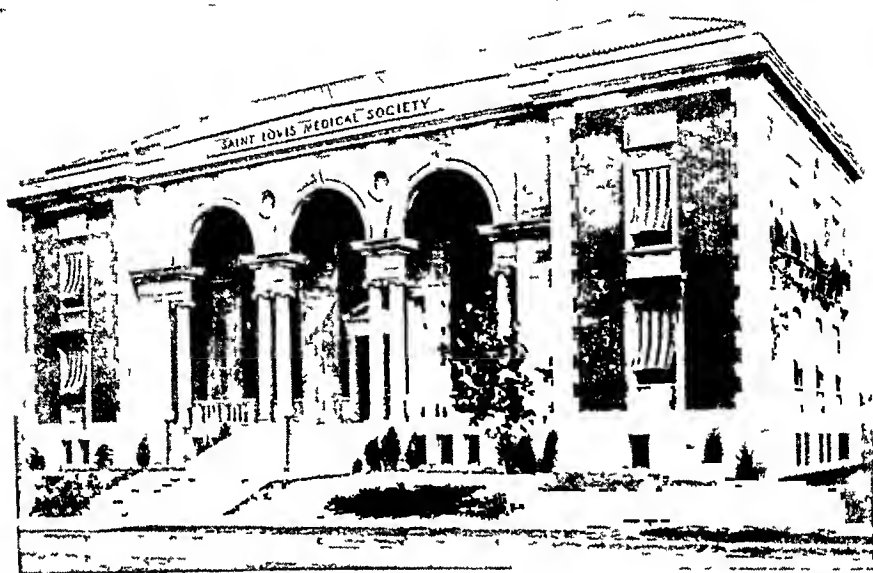


FIG 5 St Louis Medical Society

In the early days the meetings were held in the assembly room of the Public School Library in the Polytechnic Building, then on Seventh and Chestnut Streets, and later a room in the Y M C A was used.

The excellent library of the St Louis Medical Society is an outgrowth of the St Louis Medical Library Association, formerly known as the Medical Exchange Journal Club. The St Louis Medical Society moved into its beautiful new \$400,000 home at 3839 Lindell Boulevard on July 29, 1926. This building was planned and constructed especially for the convenience and comfort of the physicians of St Louis. It contains an auditorium which has a seating capacity of seven hundred, and several private meeting rooms, a dining room and adjoining rooms for entertainment.

On the walls of the first floor lobby there are tablets of Bernard Farrar, the first president of the St Louis Medical Society, William Beaumont, the pioneer American physiologist, who was president of the Society in 1841, and John Thompson Hodgen, well-known St Louis surgeon, who was president of the Society in 1876.

The library occupies the entire second floor and contains more than 30,000 volumes with 325 files of current journals and transactions in

English, French and German. A valuable collection of rare old medical books numbering about 800 volumes, with pictures of medical historical interest, was given to the Society by the late James Monroe Ball and exhibited in one of the rooms on the second floor in connection with the library.

The Bartscher room is a memorial to Dr. Hugo Bartscher from his mother, Mrs. Franciscus Bartscher. It houses many valuable historical collections, rare old medals and books, art exhibits and an excellent display of unusual photography, the work of members. On the walls are several plaques of prominent members donated by their friends in appreciation and commemoration of their valuable service to the Society. The Society has 1,000 active members. Weekly scientific meetings are held in the auditorium. The organization publishes its own weekly bulletin carrying

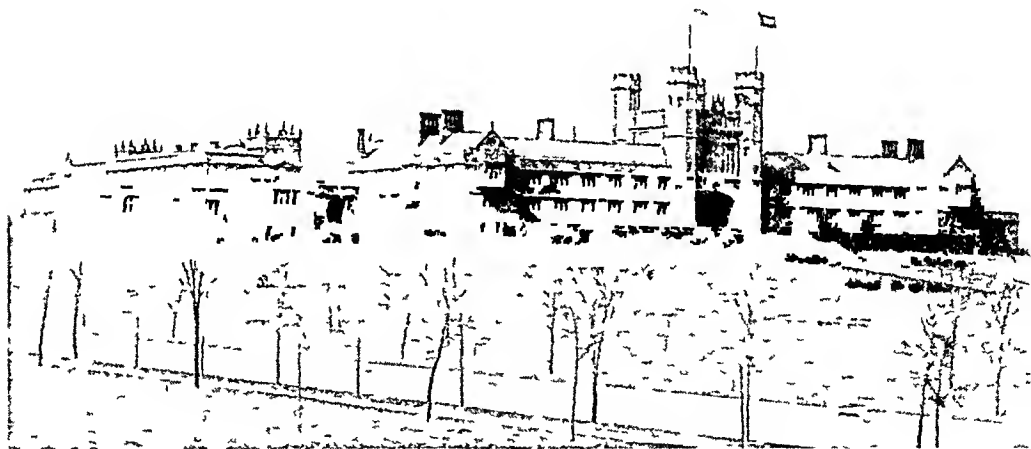


FIG 6 St. Louis University Medical School

the news of the Society, keeping its members informed as to the programs, local public health statistics, and medical news, including the proceedings of the meetings and scientific papers.

For more than three years the Society has sponsored, edited and broadcast weekly radio talks pertaining to public health matters over one of the local broadcasting stations. During the fifteen-minute program allotted through the courtesy of the station, diseases of common interest are discussed, the name of the editor and speaker being withheld. More than 170 radio talks have been broadcast.

St. Louis University School of Medicine. The School of Medicine of St. Louis University was established in 1837 in a small house on Washington Avenue between Tenth and Eleventh Streets. In 1847 the school was

affiliation between the medical school and the University was severed in 1855, and the medical department became known as the St Louis Medical College and functioned as an independent school

The Marion Sims College of Medicine, founded in 1890 and occupying a building erected for the purpose on Grand Boulevard and Caroline Street, combined in 1901 with the Beaumont Medical College, organized in 1886, and became known as Marion Sims-Beaumont Medical College In 1903 the University assumed control of these schools, which had been merged two years previously, and became known as the St Louis University School



FIG 7 The Firmin Desloge Hospital associated with St Louis University Medical School

of Medicine In the reorganization which ensued the fundamental departments, anatomy, chemistry, physiology, pathology, bacteriology and pharmacology, were placed under the direction of full-time departmental heads

The main building of the original Marion Sims College of Medicine was used until 1927, when the present medical buildings were erected The buildings are located on Compton Hill, one of the highest points in the City of St Louis, the main building facing Grand Boulevard at Caroline Street

An excellent medical library, which has been enriched by several private collections, is housed in the south wing of the building

The University Hospital, affording clinical teaching facilities to the Medical School, embraces a group of three hospitals the Firmin Desloge Hospital, St Mary's Hospital and Mt St Rose Sanitarium. The Sisters of St Mary have placed their educational and medical activities in these institutions under the complete control of the University. By an agreement between the Sisters and the University, the Directors of the various departments of the School of Medicine are made responsible for the corresponding hospital departments, thus forming a compact organization, assuring the

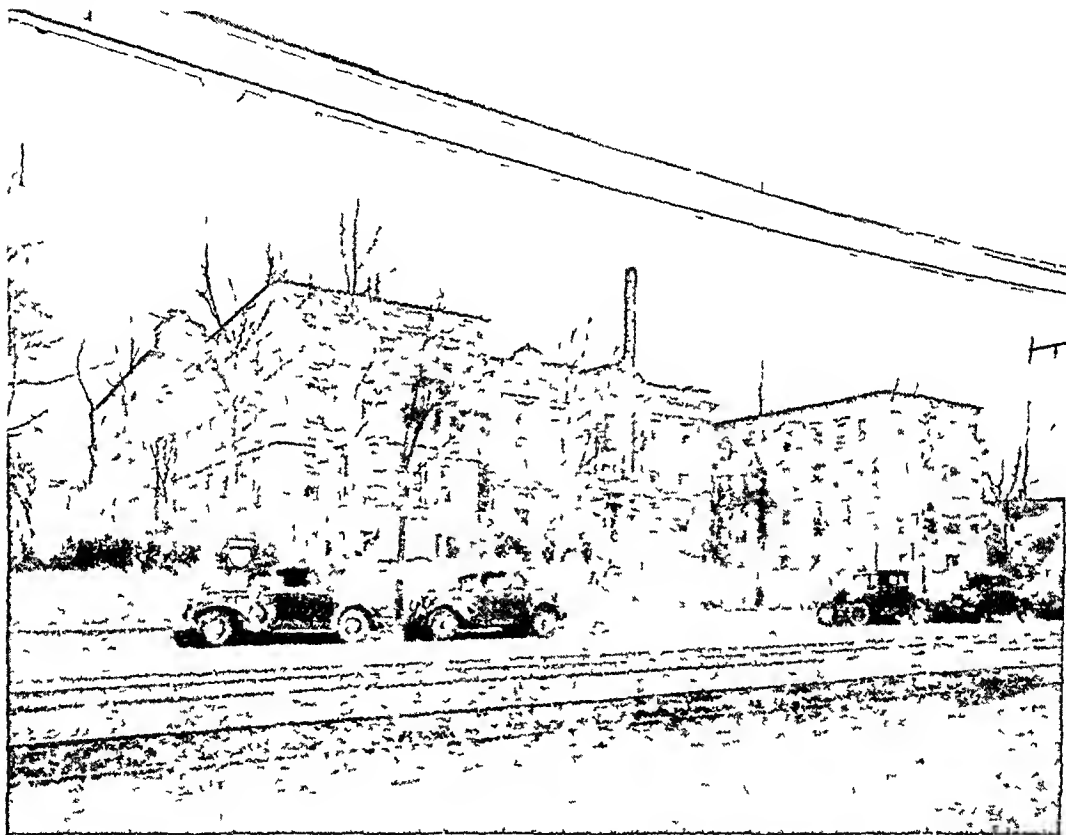


FIG 8 St Luke's Hospital

closest university supervision and the highest type of medical, educational and nursing efficiency

The Alexian Brothers', St Anthony's and St John's Hospitals are known as the "Associated Hospitals." These hospitals afford further teaching facilities and in return are given leadership and guidance in their medical and educational activities. The staffs are appointed by the University.

Intimate association is also maintained among the St Ann's Lying-In Infirmary, St Ann's Founding Society and the St Louis Obstetric Dispensary. These institutions are utilized as teaching centers for obstetrics

and pediatrics Opportunity is also afforded for teaching in the St Louis City Hospital, Isolation Hospital and St Louis City Sanitarium

Washington University School of Medicine St Louis Medical College, founded in 1842, was admitted as a department of the University in 1891 In 1899 the Missouri Medical College, which was founded in 1840, was united with the St Louis Medical College to form the medical school of Washington University This school therefore continues the work of the St Louis Medical College and the Missouri Medical College, two of the oldest medical schools west of the Mississippi River

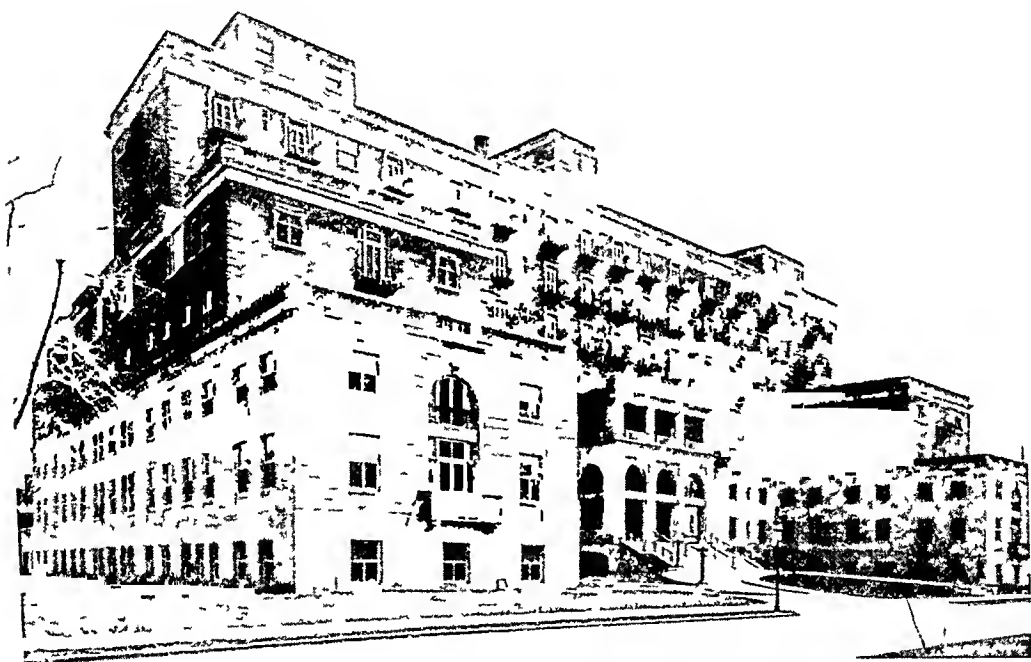


FIG 9 Jewish Hospital

In 1910, the corporation of the University, appreciating the valuable service which a medical school can render to the community, with the co-operation of the medical faculty, reorganized the school in all departments and appointed heads of departments and instructors in anatomy, physiology, biological chemistry, pathology, medicine, surgery and pediatrics, who devote themselves to teaching and research Associated with this staff are many clinical instructors chosen from the medical profession of St Louis

In 1914 the Washington University School of Medicine moved from its old location on the corner of Eighteenth and Locust Streets to the new buildings facing Forest Park on the corner of Kingshighway Boulevard and Euclid Avenue The buildings of the School of Medicine form a part of a medical group known as the Barnes Hospital group

The affiliation of Barnes Hospital, St Louis Children's Hospital, St

Louis Maternity Hospital, McMillan Eye, Ear, Nose and Throat Hospital, Mallinckrodt Radiological Institute, and Oscar Johnson Institute with Washington University School of Medicine makes these institutions for teaching purposes integral parts of the School of Medicine

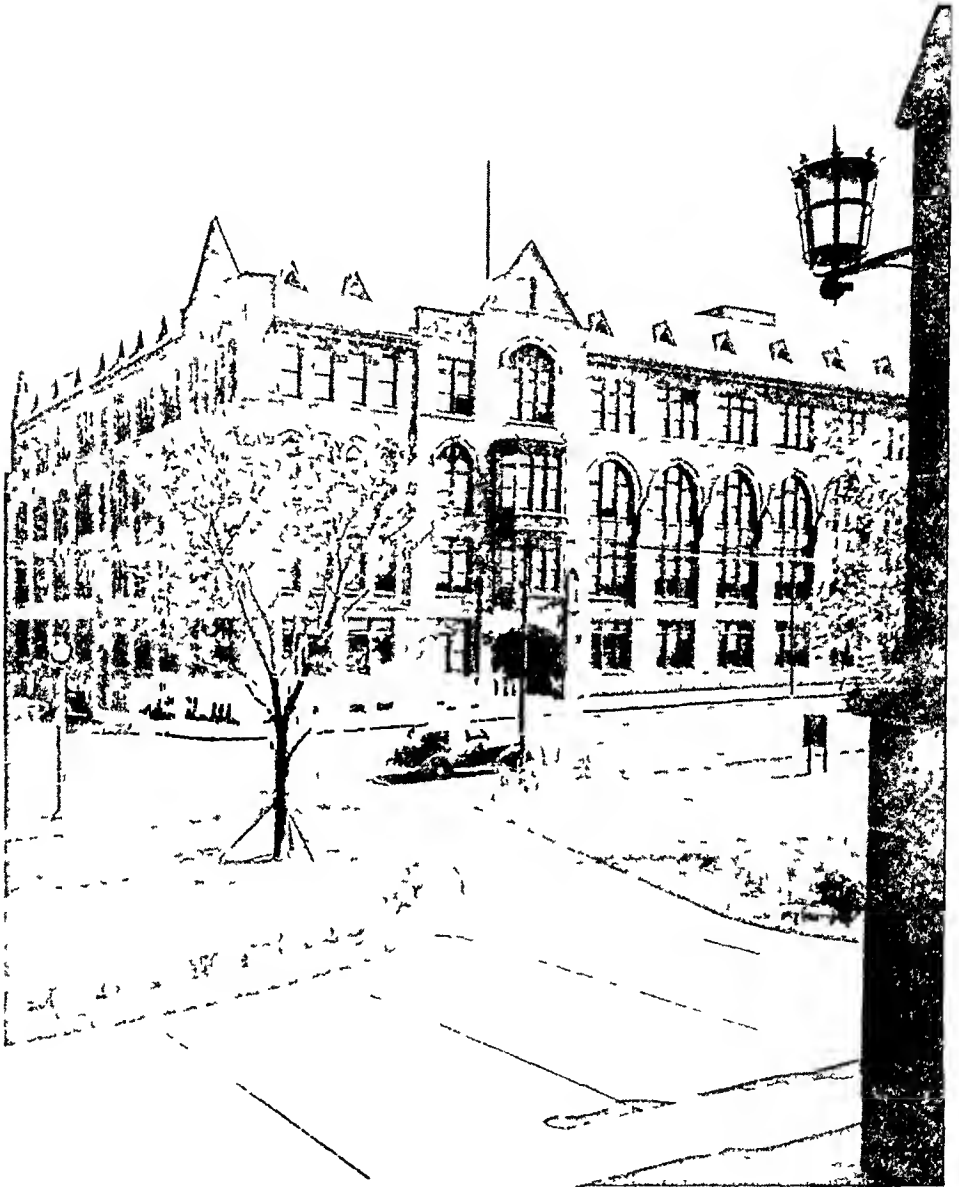


FIG 10 Washington University

The Washington University Clinics serve as an out-patient department for the University group of hospitals

Further teaching facilities are afforded by the St Louis City Hospital, including the Isolation Hospital and the City Sanitarium



FIG 11 The Medical Center at Washington University, including Barnes Hospital, St Louis Children's Hospital, St Louis Maternity Hospital, McMillan Hospital, Oscar Johnson Institute and Mallinckrodt Institute of Radiology

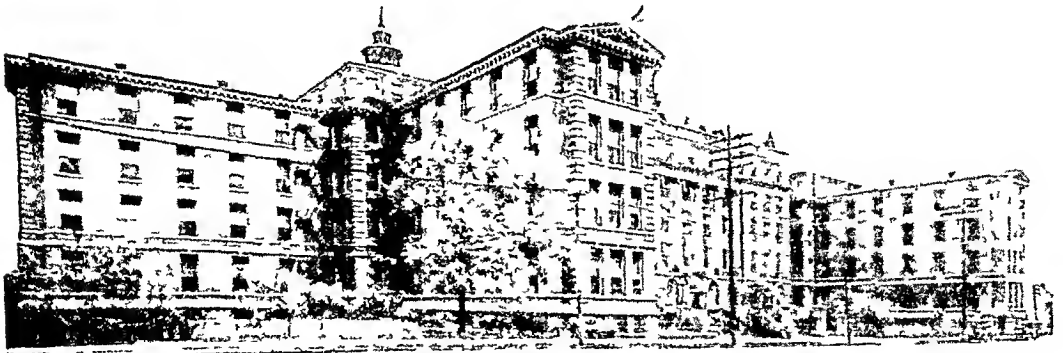


FIG 12 St Louis City Hospital

3
An excellent library is housed in the Medical School and several museums and collections for teaching and investigation are maintained by the various departments. Recently a valuable collection of anatomical specimens prepared with unusual skill and care by Bohumil Hochmann has been purchased for the museum. Diseases of bones are well illustrated by a large number of specimens collected during the early history of the school by Dr Charles A. Pope and Dr John T. Hodgen. A section of the museum contains experimental pathological lesions.

The Beaumont Room, adjoining the main reading room of the library, contains manuscripts, letters and other valuable material of the pioneer American physiologist, William Beaumont, presented to the University by his granddaughter, the late Lily Beaumont Irwin. One of the interesting items in this collection is the memorandum book containing Beaumont's original notes of the accident which befell Alexis St. Martin and made possible the renowned investigations in gastric digestion.

Independent Hospitals The hospitals which are directly connected with the two schools of medicine have already been briefly mentioned. There are numerous other excellent hospitals in St. Louis but space does not permit details concerning their many prominent features. Among these independent hospitals are the Barnard Free Skin and Cancer Hospital, Bethesda Hospital, Christian Hospital, DePaul Hospital, Evangelical Deaconess' Home and Hospital, the Frisco Employees' Hospital, Jewish Hospital, Lutheran Hospital, Missouri Baptist Hospital, Missouri Pacific Hospital, St. Ann's Widows' Hospital, St. Louis City Hospital No. 1, St. Louis County Hospital, St. Luke's Hospital, Shriners' Hospital and United States Marine Hospital.

PROGRAM
TWENTY-FIRST ANNUAL SESSION
AMERICAN COLLEGE OF PHYSICIANS
ST LOUIS, MISSOURI

April 19 to 23, 1937

GENERAL SESSIONS

Ernest B Bradley, President

ST LOUIS COMMITTEES

David P Barr, General Chairman

COMMITTEE ON ARRANGEMENTS

David P Barr, Chairman

Louis H Behrens

Jerome E Cook

Ralph A Kinsella

Alphonse McMahon

Elsworth S Smith

COMMITTEE ON CLINICS AND DEMONSTRATIONS

Ralph A Kinsella, Chairman

Harry L Alexander

Walter Baumgarten

Joseph W Larimore

Llewellyn Sale

Daniel L Sexton

Jacob Jesse Singer

COMMITTEE ON AUDITORIUM AND TRANSPORTATION

Louis H Behrens, Chairman

Jules M Brady

Joseph F Bredeck

Edwin C Ernst

Lee Pettit Gay

Frank D Gorham

William W Graves

J Curtis Lyter

Augustus P Munsch

James R Nakada

LeRoy Sante

Edwin J Schisler

Algie R Shreffler

COMMITTEE ON ENTERTAINMENT

Elsworth S Smith, Chairman

O P J Falk

Charles H Nelson

Howard A Rusk

Horace W Soper

COMMITTEE ON HOTELS

Alphonse McMahon, Chairman

Hiram S Liggett

Lionel S Luton

James F McFadden

Rudolph V Powell

August A Werner

John Zahorsky

Lee D Cady Jerome E Cook, Chairman Alfred Goldman
Charles E Gulliland

ENTERTAINMENT COMMITTEE

REGISTRATION COMMITTEE

TRANSPORTATION COMMITTEE

Mrs Harry L Alexander, Chairman	
Mrs Llewellyn Sale, Co-Chairman	
Mrs Louis H Behrens	Mrs J Curtis Lyter
Mrs Jerome E Cook	Mrs James F McFadden
Mrs Lee Pettit Gay	Mrs James R Nakada
Mrs Charles E Gilliland	Mrs Howard A Rusk
Mrs Alfred Goldman	Mrs Edwin J Schisler
Mrs Hiram S Liggett	Mrs Jacob Jesse Singer
Mrs John Zahorsky	

The City of St. Louis, the St. Louis Medical Society, the Medical Colleges of St. Louis and of Washington Universities have through their officers extended to the Fellows of the American College of Physicians a most cordial invitation to hold their 1937 Annual Session in St. Louis. The great hospitals of the City have offered their lecture halls, laboratories and wards for demonstrations and clinics. Members of the local medical profession have signified their willingness and desire to aid in the programs which have been arranged for each morning of the session.

With its two large medical schools and its numerous general and special hospitals, St. Louis offers admirable facilities for the meeting. Indeed, there are so many that it has been found impossible or at least unwise to use all of those which were made available to the committees. Consequently, the greater part of the clinical programs is to be held in only four centers—in St. Luke's Hospital, in the Jewish Hospital, and in the institutions which are associated with the two medical schools. In its teaching, St. Louis University embraces a group of hospitals which includes St. Mary's Hospital, the Mount St. Rose Sanitarium, the Alexian Brothers', St. Anthony's, and St. John's Hospitals, and the beautiful new and modern Firmin Desloge Hospital, where many of the meetings will be held. Washington University is closely affiliated with the Barnes Hospital, St. Louis Children's Hospital, St. Louis Maternity Hospital, McMillan Eye, Ear, Nose and Throat Hospital, the Mallinckrodt Radiologi-

cal Institute, and the Oscar Johnson Institute, the whole forming a medical and health center of outstanding importance. The facilities of the Barnes Hospital will be chiefly used for the meetings.

Many of the scientific discussions and clinics will be contributed by the members of the medical profession of St. Louis. Several distinguished guests, and a few of the outstanding Masters and Fellows of the College from other cities have been asked and have graciously consented to aid in the programs. While there has been scheduled each day a large number of formal programs, it is hoped that the visiting Fellows will find time to view informally the activities in the research laboratories and the points of special interest in the hospitals and medical schools. Among things which should attract particular attention are the Beaumont room of the Library at Washington University School of Medicine, which contains manuscripts, letters and other valuable original material of the pioneer American physiologist, William Beaumont, and the collection of anatomical specimens prepared by Bohumil Hochmann and housed in the museum of the anatomical department at Washington University.

St. Louis also offers to the visitor many attractions other than those of a medical and scientific nature. Among these may be mentioned the world famed Missouri Botanical Gardens, the Art Museum, the St. Louis Zoo, and the Lindbergh Trophies.

It is the sincere hope of the local committees that the St. Louis Session may be memorable among the many enjoyable and profitable meetings of the College.

WHO MAY REGISTER—

- (a) All members of the American College of Physicians in good standing for 1937 (dues, if not paid previously, may be paid at the Registration Bureau)
- (b) All newly elected members
- (c) Members of the St. Louis City Medical Society, without registration fee, upon presentation of their 1937 membership cards
- (d) Medical students pursuing courses at the St. Louis University School of Medicine and the Washington University School of Medicine, without registration fee, upon presentation of matriculation cards, or other evidence of registration at these institutions, exhibits, morning lectures and general sessions
- (e) House officers of the hospitals participating in the program, upon presentation of proper identification exhibits, morning lectures and general sessions
- (f) Members of the Medical Corps of Public Services of the United States and Canada, without registration fee, upon presentation of proper credentials
- (g) Qualified physicians who may wish to attend this Session as visitors. Such physicians shall pay a registration fee of \$12.00, and shall be entitled to one year's subscription to the ANNALS OF INTERNAL MEDICINE (in which the proceedings will be published), included within such fee.

REGISTRATION BUREAU—Temporary Registration Bureau will be open at the Jefferson Hotel on Sunday afternoon and evening, April 18. The permanent Registration Bureau will be located on the mezzanine floor of the Jefferson Hotel. Hours: 8:30 a.m. to 6:00 p.m., daily, April 19 to 23.

REGISTRATION BLANKS FOR ALL CLINICS AND DEMONSTRATIONS, MORNING LECTURES AND ROUND TABLE CONFERENCES will be sent with the formal program to members of the College. Guests will secure registration blanks at the Registration Bureau during the Session.

GENERAL INFORMATION

Headquarters

Jefferson Hotel, 12th and Locust Sts

The Jefferson Hotel will be headquarters for Officers, Regents, Governors and members of the College, also the general headquarters for registration, technical exhibits, general scientific sessions, special lectures and round table conferences

List of St Louis Hotels	No of Rooms	Blocks Removed from Headquarters	RATES PER DAY				
			ROOM—ONE PERSON		ROOM—TWO PERSONS		
			With Bath	Without Bath	With Bath	Without Bath	Suites
Jefferson Hotel, 12th and Locust	800		\$3 00-5 00 *		\$4 00-7 00		\$5 00-8 00-12 00
Chase Hotel, Lindell and Kingshighway	500	38	3 00-4 50		4 00-7 00		10 00-20 00
Congress Hotel, 275 N Union Blvd	524	40			5 00-6 00		6 00 up (Apts)
Coronado Hotel, Spring and Lindell	700	25	2 00 up		3 50 up		6 00 up
De Soto Hotel, 1014 Locust	300	1	2 00-3 00	\$1 50	3 00-4 00	\$2 50	
Forest Park Hotel, Euclid and W Pine	388	37	2 50 up		4 00 up		6 00-10 00
Kingsway Hotel, Kingshighway and W Pine	270	39	2 00 up	1 50	3 00 up		5 00 up
Lennox Hotel, 9th and Washington	400	4	2 50 up		4 00-6 00		
Mark Twain Hotel, 8th and Pine	300	6	2 50-3 50		3 50-5 50		6 00-10 00
Marquette Hotel, 18th and Washington	400	7	2 00 up	1 00-1 50	3 00 up	2 00-2 50	
Maryland Hotel, 205 N 9th	250	5	2 00-2 50	1 50	3 00-3 50	2 50	
Mayfair Hotel, 8th and St Charles	400	4	2 50-4 50		4 00-7 00		
Melbourne Hotel, Grand and Lindell	358	24	2 50-4 00		4 00-7 00		6 00-9 00
Park Plaza Hotel, 220 N Kingshighway	1100	39	3 50 up		5 00 up		
Settler Hotel, 9th and Washington	650	3	2 50-5 00		4 50-9 00		12 00
Warwick Hotel, 15th and Locust	190	3	1 50		2 50-3 00		
York Hotel, 8 S 6th	200	10	1 50 up		2 50 up		

* Also large rooms with bath for 3 or 4 persons at \$1 50 per person

BULLETIN BOARD FOR SPECIAL ANNOUNCEMENTS will be located near the Registration Bureau at the Jefferson Hotel

TRANSPORTATION—On account of recent nation-wide reductions in railroad fares, convention rates are no longer in effect. In a great many instances, however, reduced round trip tickets are in effect from certain localities. Members should consult their local ticket agents.

Special service will be available to physicians from Chicago over the Alton Railroad and from the East (New York City, Philadelphia, Wilmington, Baltimore, Washington, Martinsburg, Parkersburg, and intervening points) over the Baltimore & Ohio Railroad. Special time-tables may be obtained from the Executive Secretary, or by application to local agents of the above railroads.

THE GENERAL BUSINESS MEETING OF THE COLLEGE will be held at 5 05 p m, Thursday, April 22, immediately following the general scientific program of the afternoon. All Masters and Fellows of the College are urged to be present.

There will be the election of Officers, Regents and Governors, the reports of the Treasurer and of the Executive Secretary, and the induction to office of the new President, Dr James H Means, Boston, Mass.

BOARD AND COMMITTEE MEETINGS—The following meetings are scheduled as indicated. Special meetings will be announced and posted.

A *special dinner* will be tendered to the *Board of Governors* by members of the Board of Regents at the Jefferson Hotel, Sunday evening, April 18. An announcement of the time and place will be made later. Members of the Board of Governors are cordially invited.

COMMITTEE ON CREDENTIALS

Sunday, April 18, 9 00 a m

Room 4, Second Floor, Jefferson Hotel

BOARD OF REGENTS

Room 4, Second Floor, Jefferson Hotel

Sunday, April 18, 2 30 p m

Tuesday, April 20, 12 00 m *

Friday, April 23, 12 00 m *

BOARD OF GOVERNORS

Room 4, Second Floor, Jefferson Hotel

Monday, April 19, 5 00 p m

Wednesday, April 21, 12 00 m *

* Buffet luncheon served

SPECIAL FEATURES

MONDAY, APRIL 19, 1937

THE ANNUAL SMOKER will be given immediately following the scientific program about 10 20 o'clock in the evening in the Gold Room of the Jefferson Hotel. An interesting and amusing program has been arranged.

WEDNESDAY, APRIL 21, 1937

CONVOCATION OF THE COLLEGE—8 15 p m, Gold Room, Jefferson Hotel. All Masters and Fellows of the College and those to be received in Fellowship.

should be present Newly elected Fellows who have not yet been received in Fellowship are requested to assemble in Rooms 8 and 9, second floor (next floor above mezzanine), of the Jefferson Hotel at 7 30 o'clock, preparatory to the formation of the procession They will occupy especially reserved seats in the central section of the Ballroom, to which they will be conducted by the Convocation marshal promptly at 8 15 As this is the most formal meeting of the College, it is suggested that all appear in evening dress

The Convocation is open to all physicians and their families generally A cordial invitation is also issued to such of the general public as may be interested

Following the Convocation Ceremony, the President will present the John Phillips Memorial Medal for 1936-37 Thereafter will follow the Convocational Oration, "The Organism As a Unity," by Dr John Dewey, Professor Emeritus of Philosophy, Columbia University, New York City

The Presidential Reception will follow immediately after the program Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception

TRUDEAU CLUB LUNCHEON—The Trudeau Club of St Louis cordially invites members of the College who are especially interested in diseases of the chest to attend a luncheon at the Park Plaza Hotel at 12 30 p m on Wednesday, April 21 This will be combined with a round table discussion to be conducted by Dr James Alex Milner Because of the size of the dining room, attendance must be limited to 100 Those desiring to attend should obtain the special Round Table ticket, IV, by advance application or at the Registration Desk before Tuesday noon

THURSDAY, APRIL 22, 1937

THE ANNUAL BANQUET OF THE COLLEGE will be held in the Gold Room of the Jefferson Hotel at eight o'clock All members of the College, physicians of St Louis, and visitors attending the Session with their families are cordially invited Dr Alfred Stengel will act as Toastmaster and Dr Logan Clendening will deliver an address on "Medical Shrines" Following the banquet will occur the annual dance, to which all are invited to stay

PROGRAM OF ENTERTAINMENT FOR VISITING WOMEN

The headquarters of the visiting women will be in the Ladies Lounge on the mezzanine floor of the Jefferson Hotel A program of special features has been arranged, but ample time has been allowed for sightseeing, shopping and recreation Lists including the names of principal shops and restaurants will be issued by the local committee

MONDAY, APRIL 19, 1937

Morning Registration

Afternoon 1 30 p m A personally conducted sightseeing tour to points of interest in St Louis, to Old Cathedral, Shaw's Gardens, Lindbergh Trophies, and to the St Louis Art Museum, where Tea will be served

TUESDAY, APRIL 20, 1937

Afternoon 3 00 p m Fashion Show and Tea at the Junior League Club Cars leave Jefferson Hotel at 2 30

Evening 8 00 p m Bridge, Jefferson Hotel

WEDNESDAY, APRIL 21, 1937

Afternoon 1 00 p m Luncheon and Bridge at the St Louis Country Club Cars
leave Jefferson Hotel at 12 15
Evening 8 00 p m Convocation of the College in the Gold Room at the Jefferson
Hotel All ladies are cordially invited to attend

THURSDAY, APRIL 22, 1937

Afternoon 4 00 p m Tea given by the Woman's Club of the St Louis University
School of Medicine at the residence of Mrs Cyrus Burford
Evening 8 00 p m The Annual Banquet of the College
10 00 p m Dancing
Gold Room, Jefferson Hotel

THE EXPOSITION AND TECHNICAL EXHIBIT will be located on the mezzanine floor of the Jefferson Hotel

The exhibit will be particularly representative of the interests of Internal Medicine, and will include medical literature and texts, pharmaceutical products, apparatus and appliances, specialized physicians' furniture and many other items of special interest These exhibits will afford an opportunity for physicians to keep informed of the latest literature and the newest products in the field of medicine generally, the educational value of these exhibits should never be overlooked Furthermore, exhibitors contribute much not only to the interest of the meeting, but to the financial support of these scientific assemblies Many exhibitors have nothing to sell, but merely seek an opportunity to show what their organizations are attempting to furnish for medical science Every doctor is urged to visit each of the booths, for he will certainly find something new, interesting and scientifically valuable Special intermissions in the general program have been arranged, providing additional time for the inspection of exhibits

TECHNICAL EXHIBITORS

(Assignments up to February 10, 1937)

	<i>Space</i>
Allison Company, W D, Indianapolis, Ind	96-97
Aloe Company, A S, St Louis, Mo	72-73
American Hospital Supply Corporation, Chicago, Ill	17
Appleton-Century Company, D, New York, N Y	7
Arlington Chemical Company, The, Yonkers, N Y	8
Ayerst, McKenna & Harrison (United States) Limited, Montreal, Que	62
Aznoe's National Physicians' Exchange, Chicago, Ill	16
Baum Co, Inc, W A, New York, N Y	37
Becton, Dickinson & Co, Rutherford, N J	22-23
Bilhuber-Knoll Corporation, Jersey City, N J	29-30
Borden Company, The, New York, N Y	88
Burdick Corporation, The, Milton, Wis	80-81
Cambridge Instrument Co, Inc, New York, N Y	70
Cameron Surgical Specialty Company, Chicago, Ill	31-47
Chappel Laboratories, Rockford, Ill	15
Ciba Co, Inc, New York, N Y	38-39
Collins, Inc, Warren E, Boston, Mass	51
Davies, Rose & Co, Ltd, Boston, Mass	52
Davis Company, F A, Philadelphia, Pa	46

Davis Company, R B , Hoboken, N J	35
Dick X-Ray Company, St Louis, Mo	94-95
Doak Company, The, Cleveland, Ohio	32
Fischer & Company, H G , Chicago, Ill	98
General Electric X-Ray Corporation, Chicago, Ill	25-26-27-28
Gerber Products Company, Fremont, Michigan	87
Gradwohl Laboratories, St Louis, Mo	89
Hamilton Manufacturing Co , Two Rivers, Wis	90-91
Heinz Company, H J , Pittsburgh, Pa	64
Horlick's Malted Milk Corporation, Racine, Wis	40
Hynson, Westcott & Dunning, Inc , Baltimore, Md	65-66
Irradiated Evaporated Milk Institute, Chicago, Ill	68
Kellogg Company, Battle Creek, Michigan	4
LaMotte Chemical Products Company, Baltimore, Md	12
Lea & Febiger, Philadelphia, Pa	56
Lederle Laboratories, Inc , New York, N Y	55
Liebel-Flarsheim Company, Cincinnati, Ohio	93
Lippincott Company, J B , Philadelphia, Pa	59
Macmillan Company, The, New York, N Y	11
Mallinckrodt Chemical Works, St Louis, Mo	85-86
Maltine Company, The, New York, N Y	74
Mead Johnson & Company, Inc , Evansville, Ind	71
Medical Bureau, The, Chicago, Ill	24
Medical Case History Bureau, New York, N Y	36
Merck & Co Inc , Rahway, N J	33-34
Metropolitan Life Insurance Company, New York, N Y	6
Middlewest Instrument Company, Chicago, Ill	76
Morris & Co , Ltd , Inc , Philip, New York, N Y	79
Mosby Co , The C V , St Louis, Mo	77-78
Oxford University Press, New York, N Y	13
Patch Co , The E L , Boston, Mass	53
Petrolagar Laboratories, Inc , Chicago, Ill	14
Ralston Purina Co , St Louis, Mo	69
Rare Chemicals, Inc , Nepera Park, N Y	42-43
Sanborn Company, Cambridge, Mass	54
Sandoz Chemical Works, Inc , New York, N Y	44-45
Saunders Company, W B , Philadelphia, Pa	48
Smith, Kline & French Laboratories, Philadelphia, Pa	49-50
Spicer and Company, Glendale, Calif	2
Squibb & Sons, E R , New York, N Y	57-58
Stearns & Company, Frederick, Detroit, Mich	92
Taylor Instrument Companies, Rochester, N Y	60-61
Tebault Co , Inc , Hugh, New York, N Y	41
Vitamin Products Company, Milwaukee, Wis	75
Wander Company, The, Chicago, Ill	1
Winthrop Chemical Company, Inc , New York, N Y	9-10

GENERAL SESSIONS

Ballroom, Jefferson Hotel, St Louis, Mo

In addition to the program for the General Sessions, attention is called to the Morning Lectures and to the Round Table Discussions The programs for these two

OUTLINE OF SESSION

TIME	MONDAY April 19		TUESDAY April 20		WEDNESDAY April 21		THURSDAY April 22		FRIDAY April 23	
9 00 a m to 12 00 m	Morning free Registration, Exhibits, etc		1st Clinical Session	Morning Lectures (9 30-11 30)	2d Clinical Session	Morning Lectures (9 30-11 30)	3d Clinical Session	Morning Lectures (9 30-11 30)	4th Clinical Session	Morning Lectures (9 30-11 30)
12 00 m to 1 00 p m			Round Table Conferences		*Round Table Conferences		Round Table Conferences			
1 00 p m to 2 00 p m	Luncheon		Luncheon		Luncheon		Luncheon		Luncheon	
2 00 p m to 5 30 p m	1st General Session		3d General Session		5th General Session		6th General Session Annual Business Meeting		7th General Session	
5 30 p m to 8 00 p m	Dinner		Dinner		Dinner					
8 00 p m to 11 00 p m	2d General Session followed by Smoker		4th General Session		Convocation, followed by President's Reception		ANNUAL BANQUET and Dance			

Morning Lectures, Round Table Conferences and General Sessions will be held at Jefferson Hotel, except * Park Plaza Hotel, beginning at 12 15, Round Table 4

features are arranged to supplement the presentations given in the General Sessions. A few of the programs are arranged in the form of symposia while in others no attempt has been made to follow this plan. Some subjects have been discussed intensively—these include

Diabetes and the use of *Long-Acting Insulins*, *Endocrine Disturbances*, *Cardio-vascular Diseases*, with especial reference to *Arterial Hypertension*

Infectious Diseases are given a prominent place with the newer methods of treatment of *Streptococcal Infections*

In addition the program offers presentations on

Medical History, *Neurology*, *Gastro-enterology*, *Diseases of the Bone Marrow*, *Hodgkin's Disease* and *Hypertrophic Arthritis*. *Nutritional Disturbances* as they affect the *heart* and *thyroid* are considered

Syphilis is discussed from its *Public Health Aspect* and A Round Table discussion on its *Treatment* is provided

Thyroid Disease in the negro is discussed and there are miscellaneous papers concerned especially with *Medical Treatment*

The *Convocational Oration* will be delivered by Dr. John Dewey, Emeritus Professor of Philosophy at Columbia University. Dr. Dewey is America's foremost philosopher. He has best understood how the problems of modern life should be stated. His philosophy is a philosophy for daily use and is congenial to those attitudes that are taken instinctively by students of biology and physiology. His subject, "The Organism as a Unity," touches a point of acute interest today, the question, "What shall be the physician's attitude toward the soul-body problem, how shall there be better understanding between internist and psychiatrist?"

FIRST GENERAL SESSION

Monday afternoon, April 19, 1937

p.m.

2 00 Addresses of Welcome

George R. Throop, Chancellor of Washington University

Rev. Alphonse Schwitalla, S. J., Dean of Faculty of Medicine, St. Louis University

Curtis H. Lohr, President of the St. Louis Medical Society

Joseph F. Bredeck, Commissioner of Health, City of St. Louis

Response to Addresses of Welcome

Ernest B. Bradley, President of the American College of Physicians

2 30 The Nature and Treatment of Heart Failure

George R. Herrmann, Galveston, Tex.

2 55 The Role of the Pituitary in Carbohydrate Metabolism

Carl F. Cori, St. Louis, Mo.

3 15 INTERMISSION

4 00 Thyroid-Pituitary Relationship in Diabetes Insipidus

Thomas P. Findley, Jr., St. Louis, Mo.

4 20 Some Recent Studies on Male Sex Hormones

F. C. Koch, Chicago, Ill.

4 45 Experimental Work with the Female Sex Hormone

E. A. Doisy, St. Louis, Mo.

5 10 ADJOURNMENT

SECOND GENERAL SESSION

Monday evening, April 19, 1937

Presiding OfficerO H Perry Pepper, Philadelphia, Pa

- p m
- 8 00 Daniel Drake
Alfred Stengel, Philadelphia, Pa
- 8 30 The Physician Himself as a Therapeutic Agent
William R Houston, Austin, Tex
- 9 00 Protamine and Other Long-Acting Insulins
Russell M Wilder, Rochester, Minn
- 9 30 The Rôle of Nutritional Deficiency States in Cardiac Decompensation
Soma Weiss and Robert W Wilkins, Boston, Mass
- 10 00 The Importance of Ocular Signs in the Diagnosis of Brain Tumor
Ernest Sachs, St Louis, Mo
- 10 30 ADJOURNMENT

10 30 o'Clock

SMOKER

Ballroom, Jefferson Hotel

An interesting and amusing program has been arranged Admission by
registration badge

THIRD GENERAL SESSION

Tuesday afternoon, April 20, 1937

Presiding OfficerJames H Means, Boston, Mass

- p m
- 2 00 Practical Clinical Uses for Lactic Acid and Its Sodium Salt —
Alexis F Hartmann, St Louis, Mo
- 2 25 Healed Bacterial Endocarditis
Louis Hamman, Baltimore, Md
- 2 45 The Relief of Certain Mental Symptoms by Operation on the Frontal Lobes
with Observations upon Vasomotor and Visceral Manifestations
Walter Freeman and James W Watts, Washington, D C

3 15 INTERMISSION

4 00 The Use of Para Amino Benzene Sulphonamide or Its Derivatives in the
Treatment of Beta Hemolytic Streptococcal Infections
Perrin H Long and Eleanor A Bliss, Baltimore, Md

4 30 Bronchiogenic Carcinoma
Evarts A Graham, St Louis, Mo

5 00 ADJOURNMENT

FOURTH GENERAL SESSION

Tuesday evening, April 20, 1937

Presiding Officer

Egeiton L Crispin, Los Angeles, Calif

p m

8 00 Remarks upon the Classification of Bright's Disease and Arterial Hyper-
tension

Willard J Stone, Pasadena, Calif

8 20 The Hereditary Factor in Essential Hypertension

Edgar A Hines, Jr, Rochester, Minn

8 40 Further Studies in the Genesis and Surgical Treatment of Essential Hyper-
tension

George W Crile, Cleveland, Ohio

9 10 Experimental Hypertension Due to Renal Ischemia

Harry Goldblatt, Cleveland, Ohio

9 40 The Surgical Treatment of Peptic Ulcer

Irvin Abell, Louisville, Ky

10 00 ADJOURNMENT

FIFTH GENERAL SESSION

Wednesday afternoon, April 21, 1937

Presiding Officer

David P Barr, St Louis, Mo

p m

2 00 The Clinical Caprices of Hodgkin's Disease

William S Middleton, Madison, Wis

2 25 Hyperthyroidism in the Negro

William B Porter, Richmond, Va

2 50 The Nutritional Factor in Graves' Disease

James H Means, Boston, Mass

- 3 10 INTERMISSION
 3 55 Recent Knowledge Concerning Influenza
 Richard E. Shope, Princeton, N. J.
 4 25 The Internist and Syphilis Control
 Hugh J. Morgan, Nashville, Tenn.
 4 50 A Study of the Diagnosis and Treatment of Lobar Pneumonia According to
 Types and Specific Serum Therapy
 Julien E. Benjamin and Marion A. Blankenhorn, Cincinnati, Ohio
 5 10 ADJOURNMENT

ANNUAL CONVOCATION

Wednesday evening, April 21, 1937

8 30 o'clock

Ballroom, Jefferson Hotel

All members of the profession and the general public are cordially invited. No special admission tickets will be required.

- 1 Presentation of newly elected Fellows and recital of the Pledge
 William Gerry Morgan, *Secretary-General*, Washington, D. C.
- 2 Conferring of Fellowships, and Address
 Ernest B. Bradley, *President*, Lexington, Ky.
- 3 Presentation of the John Phillips Memorial Medal for 1936-37
- 4 Convocation Oration "The Organism as a Unity"
 John Dewey, Professor Emeritus of Philosophy, Columbia University, New York, N. Y.

President's Reception

The Reception will follow immediately after the program. Newly inducted Fellows should sign the Roster and secure their Fellowship Certificates during the Reception.

SIXTH GENERAL SESSION

Thursday afternoon, April 22, 1937

Presiding Officer

William Gerry Morgan, Washington, D. C.

p m

- 2 00 Bone Marrow Biopsies: A Development of the Diagnostic Procedure
 Edward L. Tuohy, Duluth, Minn.

- 2 20 The Differential Diagnosis and Therapeutic Rationale of Diseases Primarily Involving the Bone Marrow
Charles A Doan, Columbus, Ohio
- 2 45 The Occurrence and Treatment of Arrhythmias in Coronary Artery Thrombosis
Arthur M Master, New York, N Y
- 3 10 Early Clinical Recognition of Disturbances in Heart and Blood Vessel Pathology—As Possible Solution to High Cardiac Mortality Rate
Clarence L Andrews, Atlantic City, N J
- 3 30 INTERMISSION
- 4 15 What is Hypertrophic Arthritis?
Walter Bauer, Boston, Mass
- 4 45 The American Board of Internal Medicine and Certification of Internists
Walter L Bierring, Des Moines, Iowa
- 5 05 ADJOURNMENT

The *Annual Business Meeting* of the College will be held immediately after the last paper. All Masters and Fellows are urged to be present. Important amendments to the Constitution and By-Laws of the College are to be presented for consideration and adoption. Official reports from the Treasurer and Executive Secretary will be read, new Officers, Regents and Governors will be elected, and the President-Elect, Dr James H Means, will be inducted into office.

Thursday evening, 8 00 o'Clock

Ballroom, Jefferson Hotel

THE ANNUAL BANQUET OF THE COLLEGE

(Procure Tickets at the Registration Bureau)

Consult Special Banquet Program

Toastmaster Alfred Stengel, Philadelphia, Pa

Address "Medical Shrines"

Logan Clendenen, Professor of Clinical Medicine, University of Kansas
School of Medicine, Kansas City, Mo

Dancing

SEVENTH GENERAL SESSION

Friday afternoon, April 23, 1937

Presiding Officer

Hugh J Morgan, Nashville, Tenn

p m

2 00 The Dementia Precox Problem
Gustave W Dishong, Omaha, Nebr

- 2 20 The Liver in Thyroid Disease
Elmer C Bartels, Boston, Mass
- 2 50 Epigastric Hernia
Louis A M Krause and David Tenner, Baltimore, Md
- 3 15 INTERMISSION
- 3 35 The Chemical Constitution of Gastric Juice and an Estimate of the Value
of Gastric Secretory Studies in Clinical Medicine
Lay Martin, Baltimore, Md
- 3 55 Electrocardiographic Changes in Dogs Following External Injury
Ray W Kissane, Columbus, Ohio
- 4 15 Ebstein's Disease or Congenital Dislocation of the Tricuspid Valve, Report
of a Case with Intraventricular Conduction Disturbances Studied by
Serial Sections Through the Conduction System
Wallace M Yater, Washington, D C, and Morse J Shapiro, Minneapolis,
Minn
- 4 35 ADJOURNMENT

PROGRAM OF MORNING LECTURES

This course of Morning Lectures is a special feature on the program, arranged at the request of a large number of members. The course is presented as an elective, as a whole or for individual days, in place of hospital clinics. Those attending the lectures may also attend the Round Table Conferences. These lectures will be presented daily, Tuesday to Friday, inclusive, from 9 30 to 11 30 a m in the Ballroom of the Jefferson Hotel.

It is intended that the Morning Lectures shall be highly practical, and that the speakers will present their subjects with the aid of lantern slides, moving pictures and other demonstrations. They will consist of three symposia: Tuberculosis, Infectious Diseases and Diabetes Mellitus, and a mixed program.

The lectures will be open to all members of the College, guests of the College, members of the St Louis Medical Society, Senior students of the medical schools of St Louis and House Officers of participating hospitals. *Admission by regular registration badge*

Tuesday Morning, April 20, 1937

ML 1

JEFFERSON HOTEL

Ballroom

Symposium on Tuberculosis

- 9 30-10 00 Recent Studies Bearing on Tuberculous Infection and Reinfection
Henry C Sweaney, Chicago, Ill
- 10 00-10 30 Heliotherapy and Tuberculosis
Edgar Mayer, New York, N Y
- 10 30-11 00 Surgical Measures in Treatment of Tuberculosis
Ralph C Matson, Portland, Ore
- 11 00-11 30 The Prognosis in Tuberculosis
F M Pottenger, Monrovia, Calif

Wednesday Morning, April 21, 1937

ML 2

JEFFERSON HOTEL

Ballroom

Symposium on Infectious Diseases

- 9 30-10 00 Chronic Brucella Infections
Fred E Angle and William H Algie, Kansas City, Kan
- 10 00-10 30 The Clinical Types of Encephalitis
Theodore C Hempelmann, St Louis, Mo
- 10 30-11 00 Scarlet Fever
Jean Valjean Cooke, St Louis, Mo
- 11 00-11 30 Meningococcic Meningitis and Meningococcemia
Josephine B Neal, New York, N Y
-

Thursday Morning, April 22, 1937

ML 3

JEFFERSON HOTEL

Ballroom

Symposium on Diabetes

- ✓ 9 30-10 00 Clinical Use of Crystalline Insulin
Samuel S Altshuler, Detroit, Mich
- ✓ 10 00-10 30 Treatment of Diabetes Mellitus with Insoluble Insulin Compounds,
II Histone-Insulin
Percival A Gray, Jr, Fritz Bischoff and William D Sansum, Santa
Barbara, Calif
- 10 30-11 00 Factors Influencing the Prognosis in Diabetic Coma
Edward S Dillon and W Wallace Dyer, Philadelphia, Pa
- 11 00-11 30 The Hemopoietic Liver Principle
George E Wakerlin, Louisville, Ky
-

Friday Morning, April 23, 1937

ML 4

JEFFERSON HOTEL

Ballroom

- ✓ 9 30-10 00 Sedimentation Rate of the Blood and Its Application in Clinical
Medicine
Edwin G Bannick, Rochester, Minn
- 10 00-10 30 Inquiries into the Fundamental Nature of Disease
John W Williams, Cambridge, Mass
- 10 30-11 00 Subacute Bacterial Endocarditis Active Cases with Negative Blood
Cultures
Chester S Keefer, Boston, Mass
- 11 00-11 30 The Less Common Varieties of Hypertension
Maurice C Pincoffs, Baltimore, Md

ROUND TABLE CONFERENCES

This series of Round Table Conferences is a new feature on the program of the Annual Session of the College. These Round Tables have been scheduled at a time so as not to conflict with the Morning Lectures or the Hospital Clinics.

A national authority has been selected for each topic. Three Round Tables will be in progress simultaneously, and all will be held in adjoining rooms at the Jefferson Hotel, with the exception of the one on Pulmonary Tuberculosis, which will be held at the Park Plaza Hotel. The groups will necessarily be restricted in attendance.

Special tickets, similar to the Clinic tickets, will be required for each Round Table. When application is made for a Round Table it is strongly urged that the *applicant submit in writing a question or topic which he wishes discussed.* These questions will be given in advance to the Leaders of the Round Tables who will discuss such subjects as seem most in demand.

PROGRAM OF ROUND TABLES

Tuesday, April 20, 1937

JEFFERSON HOTEL

Second Floor, Room 9

(Capacity, 100)

- 12 00 m-1 00 p m I ROUND TABLE on Diabetes Mellitus
 Leader Elliott P Joslin, Clinical Professor of
 Medicine at the Harvard University Medical
 School, Medical Director of the George F Baker
 Clinic, New England Deaconess Hospital, Bos-
 ton, Mass

JEFFERSON HOTEL

Second Floor, Room 8

(Capacity, 80)

- 12 00 m-1 00 p m II ROUND TABLE on the Public Health Aspects of
Syphilis
 Leader Thomas Parran, Surgeon-General, United
 States Public Health Service, President of the
 American Public Health Association, Washing-
 ton, D C

JEFFERSON HOTEL

Second Floor, Room 7

(Capacity, 80)

- 12 00 m-1 00 p m III ROUND TABLE on Cardiovascular Problems
 Leader Samuel A Levine, Assistant Professor of

Medicine, Harvard University Medical School,
Senior Associate in Medicine, Peter Bent Brigh-
ham Hospital, Boston, Mass

Wednesday, April 21, 1937

PARK PLAZA HOTEL

(200 N Kingshighway)
(near Washington University and Barnes Hospital)

(Capacity, 100)

- 12 15 p m - 1 00 p m IV ROUND TABLE on Pulmonary Tuberculosis
Leader James Alex Miller, Professor of Clinical
Medicine, Columbia University College of Phy-
sicians and Surgeons, Visiting Physician and
Physician in Charge of Tuberculosis Division,
Bellevue Hospital, New York, N Y
Followed by luncheon as guests of the Trudeau So-
ciety of St Louis
-

JEFFERSON HOTEL

Second Floor, Room 9

(Capacity, 100)

- 12 00 m - 1 00 p m V ROUND TABLE on Gastro-Enterologic Topics
Leader Walter C Alvarez, Head of Section, Di-
vision of Medicine, The Mayo Clinic, and Pro-
fessor of Medicine in the University of Minne-
sota, Graduate School of Medicine, Rochester,
Minn
-

JEFFERSON HOTEL

Second Floor, Room 8

(Capacity, 80)

- 12 00 m - 1 00 p m VI ROUND TABLE on Amebiasis and Malaria, Diag-
nosis and Treatment
Leader Henry E Meleney, Associate Professor of
Preventive Medicine and Public Health, Vander-
bilt University School of Medicine, Nashville,
Tenn

Thursday, April 22, 1937

JEFFERSON HOTEL

Second Floor, Room 7

(Capacity, 80)

- 12 00 m-1 00 p m VII ROUND TABLE on Allergy
 Leader Robert A Cooke, Assistant Professor of
 Clinical Medicine, Cornell University Medical
 College, Consultant in Medicine, New York Hos-
 pital, Director, Department of Allergy, Roosevelt
 Hospital, New York, N Y

JEFFERSON HOTEL

Second Floor, Room 9

(Capacity, 100)

- 12 00 m-1 00 p m VIII ROUND TABLE on Diseases of the Blood
 Leader O H Perry Pepper, Professor of Medicine,
 University of Pennsylvania School of Medicine
 Philadelphia, Pa

JEFFERSON HOTEL

Second Floor, Room 8

(Capacity, 80)

- 12 00 m-1 00 p m IX ROUND TABLE on the Treatment of Various
Phases of Syphilis
 Leader Udo J. Wile, Professor of Dermatology
 and Syphilology, University of Michigan Medi-
 cal School, Ann Arbor, Mich

Please NOTE that all Round Tables are to be held at the Jefferson Hotel,
 except the Round Table on Tuberculosis, which is to be held at the Park Plaza
 Hotel

SPECIAL CLINICS AND DEMONSTRATIONS

Clinics and demonstrations will be held in the forenoons from 9 30 to 12 00
 daily, Tuesday to Friday, inclusive

Tickets will be required for each and every one of the special clinics, ward
 rounds and demonstrations. The cooperation of every one in securing his clinic
 tickets will assist greatly in distributing the attendance according to the capacity
 of each program. It is self-evident that an exercise arranged for fifteen will lose

its value for all if fifty crowd in Ticket registration is the only effective method of keeping the attendance within the capacities indicated

The clinics and demonstrations will be held in the Barnes Hospital, F. M. Desloge Hospital, Jewish Hospital, St. Luke's Hospital, St. Louis University Medical School and Washington University School of Medicine. The full detail of the program will be made available shortly after the appearance of this issue of the ANNALS. From the preliminary notices it is apparent that a very well organized series of clinical meetings will be offered by each institution. There are to be excellent symposia on allergy, endocrine diseases, peripheral vascular disease, hypertension, diseases of the blood, fever therapy, diabetes, diseases of the lungs, emphysema and numerous other clinics and demonstrations covering a wide range of topics in the infectious diseases, diseases of the digestive tract, of the nervous system, etc. In many of these features the staffs of the institutions concerned have added guest speakers of note from other parts of the country. It is felt that the clinical program of this meeting will meet or surpass the highest standards set in previous sessions of the College.

ANNALS OF INTERNAL MEDICINE

VOLUME 10

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NUMBER 10

THE THYREOACTIVATOR HORMONE, ITS ISOLATION FROM THE ANTERIOR LOBE OF THE BOVINE PITUITARY GLAND AND ITS EFFECTS ON THE THYROID GLAND

By EDUARD UHLENHUTH, *Baltimore, Maryland*

THE results of the work to be summarized here and leading to the conclusion that the anterior pituitary manufactures and excretes a specific thyreoactivator hormone by means of which the hypophysis controls the activity of the thyroid, were reported first, by Uhlenhuth and Schwartzbach, in 1926, at the annual meeting of the American Zoologists in Philadelphia.³ A brief account covering all the essential points of evidence was published by Uhlenhuth and Schwartzbach, in 1927.

The history of investigations pertaining to the subject with which the present article is dealing, has been discussed briefly, yet in its most essential features, in "Endokrinologie, 1935, xv, 329-342", in the latter article as well as in many other articles due credit has been given to those who preceded the author. It is for this reason and because of the limitations of space that the author had to omit all references to the work of other investigators.

As we were guided in our work on the thyreoactivator by previous comparative studies of the structure of the thyroid of amphibians (salamanders) and as these morphological studies had yielded important results concerning the functional significance of certain structures of the thyroid and concerning the biological evaluation of pathological conditions of the human thyroid, these comparative morphological studies will appropriately

* Van Meter Prize Essay, 1936. Read before the American Association for the Study of Goiter, June 9, 1936.

From the University of Maryland Medical School.

The work reported in this essay was conducted under the auspices of the Medical School of the University of Maryland, and with the collaboration of the author's students and associates. Financial aid was received from the "Julius Friedenwald Fund for Medical Research," from the "Weaver Fund" and from the "Hitchcock Fund," all three of the University of Maryland Medical School, from the "Elizabeth Thompson Science Fund" of Harvard University and from a gift received personally by the author through the generosity of Mr. Victor Bloede of Baltimore.

form the introduction to our physiological experiments. In order to emphasize that, although we can submit ample evidence indicating a humoral control of thyroid activity, we nevertheless do not believe that the nervous system has no part in regulating thyroid activity, a report of our recent investigations bearing on the nervous control of the thyroid, is appended.

I A FUNCTIONAL INTERPRETATION OF THYROID STRUCTURE

At the time when we became interested in the study of the thyroid gland, a satisfactory functional interpretation of the thyroid structure was not available, in spite of the splendid work of anatomists, physiologists, and clinical scientists such as R. B. Benslev, David Marine, McCallum, Allen Graham, Louis Wilson and others. In fact there was no agreement as to the structural picture of a highly active, as contrasted to a relatively dormant, thyroid. There was even no general consent as to the significance of the thyroid colloid. Many reports appeared at that time maintaining that a scarcity of colloid indicates a low activity, while some English

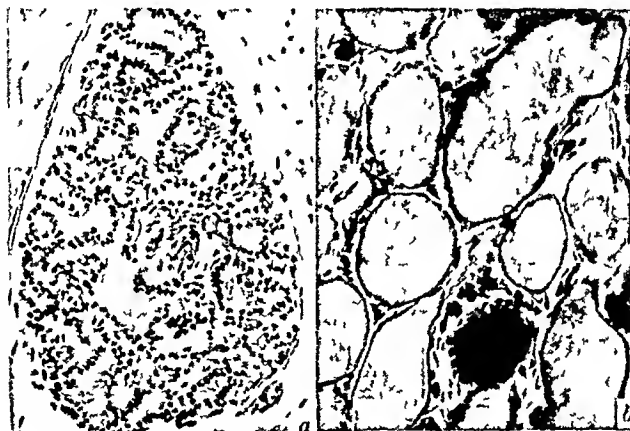


FIG 1 Showing two different thyroid types of adult salamanders of two different species (same magnification). (a) Gland of adult marble salamander during spring activity, resembling exophthalmic goiter, note star-shaped follicles and numerous colloid vacuoles. (b) Gland of aquatic Colorado axolotl, resembling colloid goiter, note large roundish follicles and absence of colloid vacuoles. (From Roux's Arch., 1927, CIV, 611, figures 27 and 34.)

surgeons (Williamson and Pearse) contended that the colloid is a waste product which, once deposited, never again leaves the lumen of the follicle.

It appeared to us that many of these important questions could be answered, by studies of the thyroid in a group of animals in which this gland normally presents a wide variety of functional states and structural types. Such a group of animals presented itself to us in the so-called salamanders or tailed amphibians. In these animals thyroids ranging from the structure of a human exophthalmic goiter gland to that of a human colloid goiter are found normally (figure 1). It was soon discovered, moreover, that closely allied species and even varieties of the same species possessed widely differing thyroids which not only represented a fixed and

inherited type characteristic for each variety, but were associated with a biology which could be traced back to the functional level of the particular thyroid type. In addition these animals had been previously found to react promptly, when in an aquatic stage, upon administration of thyroid with transformation (metamorphosis) into a terrestrial stage (Gudernatsch, 1913). In this peculiarity a simple means is afforded to use metamorphosis as a test for thyroid activity. Hence an extensive study of the thyroid of salamanders was undertaken. A detailed account of this work was published in 1927.⁵ The essential results of this work are the following:

(a) *The Colloid Plays an Essential Rôle in the Specific Function of the Thyroid*. It was found that during developmental stages at which the thyroid does not function, colloid is stored in the follicles. At the beginning of a functional period it is suddenly, within 24 hours, released from the follicles, but is stored again when the functional period has passed. In a quantitative study of 40 thyroids the total mass of thyroid tissue, the mass of epithelium and the mass of colloid could be expressed in gram weight.* In the graph of figure 2 are shown the absolute weights of the colloid and of the epithelium. It is noticed that during the inactive period colloid is stored, while during the functional period 50 per cent of the stored colloid is released suddenly, several days later the follicles are refilled and the mass of colloid again increases. The same events are shown in figure 3 in which the amount of colloid is expressed in percentages of the total thyroid mass. Evidently colloid is released precisely at the time of thyroid activity. The release of the stored colloid is an essential feature of thyroid activity, the colloid is essential in the specific function of the thyroid gland.^{1, 2}

(b) *Structural Characters of Active and Dormant Thyroid*. Selecting different developmental stages of the thyroid of the same species, and studying, furthermore, the thyroids of different species in which the degree of thyroid activity could be determined by its physiological effects on the biology of the species, we are able to recognize structural characters distinguishing the active from the dormant thyroid.⁵ These are

<i>Active Thyroid</i>	<i>Resting Thyroid</i>
(1) Stainable colloid absent or scarce	Large quantities of stainable colloid
(2) Walls of follicles collapsed, shape of follicles star-like (with papillae and solid cell columns)	Follicles roundish, with regular outlines
(3) Colloid vacuoles numerous	Colloid vacuoles scarce or absent
(4) Cells enlarged and swollen	Cells small and flat
(5) Cells filled with secretion vacuoles (for which we introduced the term "Anderson Vacuoles")	Cytoplasm not vacuolized

In figure 4 are shown the patterns of an active and of a dormant gland of the same species, elucidating points 1 and 2. The difference in the number of colloid vacuoles, existing between an active and an inactive gland is brought out well in figure 1. In figure 5 are illustrated the increase in

* For details of technique see "W. Roux's Arch. f. Entwicklgsmech., 1927, civ, 616."

Figure 2

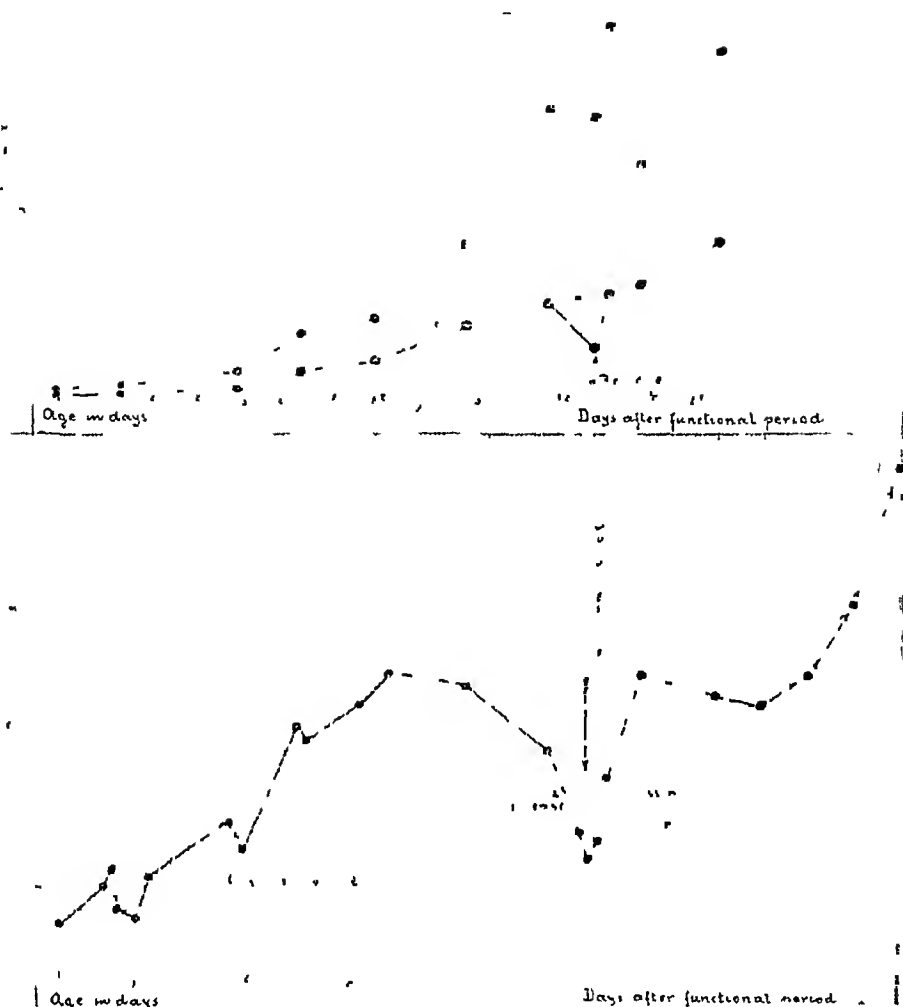


Figure 3

FIG 2 Showing a functional cycle of the thyroid, with increasing amounts of colloid during "Storage" phase, and colloid release (drop in the lower one of the two curves) during "Releasing" or active phase

FIG 3 Showing the functional cycle of the thyroid, colloid expressed in percentages of total thyroid weight, emphasizing the sharp drop in colloid amount during the "Releasing phase," relative to the other thyroid tissues (See Roux's Arch, 1927, civ, 620, table 2)

the cell size and the vacuolization of the cytoplasm so characteristic of the active thyroid

(c) *The "Two-Phase Cycle" of Thyroid Activity* In studying the periods of thyroid activity in one species and correlating them with the corresponding structural appearances it was found that thyroid activity is cyclic and that the entire cycle consists of two phases, a "storage phase" and a "releasing phase" During the former the cells manufacture actively the colloid, excreting it, however, only in one direction, into the lumen of

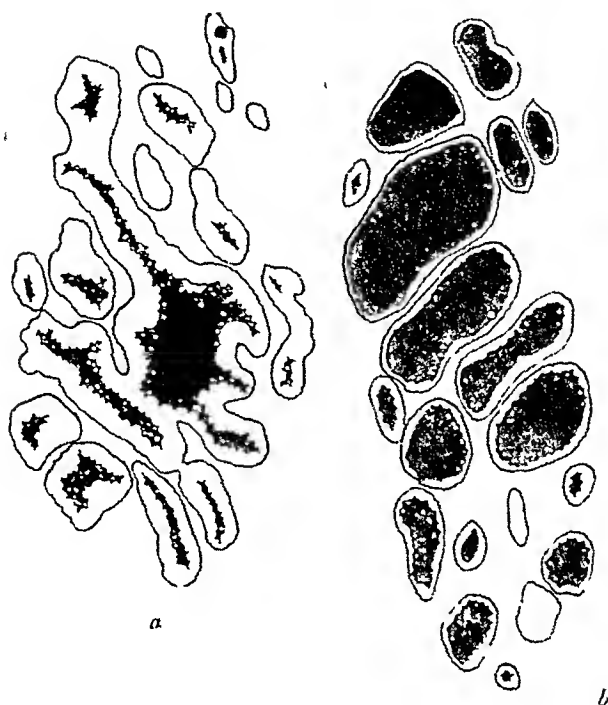


FIG 4 Showing changes in thyroid pattern during functional cycle of thyroid of same species (a) "Releasing phase," during height of spontaneous (physiological) activity (b) "Storage phase" during dormant period (Redrawn from Roux's Arch, 1927, cix, 611)



FIG 5 Cells of (a) dormant (storage phase) and (b) active (releasing phase) thyroid, at same magnification Note increased cell size and presence of intracellular secretion vacuoles in active gland (Redrawn from figures 72 and 61 in Roux's Arch, 1927, cix, 611)

the follicle where it is stored and eventually leads to a distention (figures 4b and 1b), or even bag-like enlargement of the follicles. During the latter phase the colloid is allowed to escape from the follicles into the blood stream, if the release takes place at a faster rate than the manufacture of colloid, the follicles collapse and assume a star-like shape, the lumina of the follicles changing into mere slits (figure 4a). As the physiological effects of the thyroid hormone are apparent only during the releasing phase of the cycle, the terms "active" or "activated" will be applied henceforth only to thyroids which are in the releasing phase.

(d) *Releasing Factor* On the basis of differential reactions to iodine as observed by Swingle in frogs, and in salamanders in our own laboratory, and guided by the behavior of species in which the thyroid remains permanently in the storage phase, we were led to the conclusion that only the

storage phase is controlled by the thyroid's own, intrinsic powers, while the releasing phase is caused by the effects, upon the thyroid, of an extrinsic agent which we called at that time the "releasing factor" and the nature of which was unknown to us. Our evidence seemed to suggest that the manufacture of colloid and its excretion into the lumen of the follicles are primary and essential functions of the thyroid cells and going on continuously, their rate being dependent only on the degree of distention of the follicles, but that the unique peculiarity of the thyroid, its closed vesicles, has called forth the development of a special extrinsic mechanism controlling the release of the stored secretion from these vesicles.⁵

(e) *Interpretation of Human Thyroid Pathology* A comparison of different types of salamander thyroids with human pathologic thyroids immediately revealed striking resemblances, especially between exophthalmic goiter and the "releasing type" on the one hand, and between colloid goiter and the "storage type" on the other hand. These resemblances were expressed in nine structural and three functional points for exophthalmic goiter, and in eight structural points for colloid goiter. Since it appeared that the two types are merely different stages of one functional cycle and the normal responses of the thyroid to corresponding stimuli, the conclusion seemed unavoidable that in man likewise these two thyroid types could not be considered as the result of a pathological thyroid, but would, on the contrary, indicate the presence of a normal thyroid in the possession of all its normal potentialities and capable of responding normally to the presence or absence of the extrinsic releasing factor. It was suggested that in the case of exophthalmic goiter the disturbance might have to be looked for in the extrinsic releasing factor which in this case appeared to be working overtime ("p. 732").

The evidence in our hands concerning the existence of an extrinsic releasing factor was so convincing that a vigorous search was begun immediately. These studies which were conducted in collaboration with S. S. Schwartzbach, led finally (summer, 1926) and after three years of entirely unsuccessful work with nerve stimulating drugs, to the discovery of the thyreoactivator.

II HUMORAL EXCITATION OF THE THYROID GLAND

Up to 1926 no agent was known by which an artificial stimulation of the thyroid gland could be effected. Our task, as we saw it then, was that of finding a substance by means of which the thyroid could be forced experimentally from the storage phase into the releasing phase, producing thus a thyroid type which would exhibit the essential structural features of this gland at the height of its releasing activity and would therefore resemble the thyroid of a metamorphosing salamander or the human exophthalmic goiter gland.

The results of this work may be summarized under the following points

(a) *The Extraction of the Thyreoactivator (TA)* In our first experiments conducted together with Schwartzbach,^{4,7,8,9,10} three different kinds of bovine pituitary anterior lobe (AL) powder were used. Armour's commercial desiccated AL, and AL powder prepared according to our prescriptions, especially for us by Armour & Co¹, and a powder prepared by ourselves. At present all powders are prepared in our own laboratory by the following method.

The anterior lobes are separated from the posterior lobes by ourselves in the abattoirs,⁷ not later than 40 minutes after the death of the animals. So far only steer pituitaries have been used. Immediately after arrival in the laboratory the glands are cut into small pieces, spread on glass plates and air-dried overnight, by electric fans. If properly manipulated, the glands, neither after this procedure nor at any time later, exhibit any odor of putrefaction. The air-dried material is then desiccated for six days over calcium chloride, ground through a 40 mesh sieve, placed in glass-stoppered bottles and kept, over calcium chloride, in a refrigerator. This powder retains its effectiveness for at least six months.

The powders were extracted, in our first experiments, in acidified Ringer solution (0.5 c.c. of glacial acetic acid per 100 c.c. Ringer) and only occasionally in plain Ringer, the extraction being performed by heating the mixture just to the boiling point. At present plain Ringer is used and the extraction is carried out as follows. A quantity of powder is added to the Ringer solution in such proportions that the final extract will contain TA equivalent to 25 to 200 mg. of dried powder per 0.5 c.c. fluid. The mixture is carefully heated until it almost boils, is filtered immediately, taken up into a syringe and injected as soon as possible.

The appearance of such an extract is that of a clear and markedly pinkish fluid. If the mixture is watched during the process of heating, it is observed that when a temperature close to the boiling point is reached, a loose and flocculent precipitate appears, mingling with the powder particles. On standing the entire mass rises while previous to the formation of this precipitate the AL particles sink to the bottom.

In more recent experiments to be published elsewhere, extracts were prepared by permitting the mixture to stand overnight in a refrigerator and filtering it without heating. Filtration in this instance proceeds very slowly as the fluid is of thick, syrupy consistency. If, after filtration, this fluid is heated, the same loose precipitate observed with the previous technic will form. Extracts prepared by the technic of cold extraction contain thyreoactivator, but we do not know as yet what yield can be obtained by this method. We suspect that it does not result in a separation of the TA from the other hormones contained in the AL.

When extracts prepared by heating are cooled on ice or are permitted to stand for several hours, a fine precipitate falls. Although we have not made specific tests we are under the impression that cooling or standing decreases the strength of the extract.

When the powder is extracted in acidified Ringer, neutralization by N/10 NaOH is necessary. If this is carried beyond a certain point, a precipitate begins to form. Edgar Van Slyke found that the precipitate appears at a pH of 6.8. In experiments conducted together with Norman Wilson we found that extracts precipitated with NaOH and filtered free of the precipitate, have practically lost their power of meta-

* The author takes great pleasure in acknowledging here the valuable assistance and cooperation rendered in this phase of the work by Dr. Frederick Fenger of Armour and Co.

† The author, in behalf of his students and the University of Maryland, wishes to express his gratitude to Mr. Robert Fox, of Greenwald and Company, Baltimore, for the fine spirit of cooperation and generosity which he and his firm have shown to us throughout our work and which in no small measure have made possible our success.

morphosing the larval salamanders, suggesting that the precipitate carries down the TA

Although we have not attempted chemical purification of the extracts, we succeeded, nevertheless, by the simple technic of heating the extracts, in isolating the TA from most of the other AL hormones. The gonads of hundreds of animals were examined, never have we observed gonadotropic effects of our extracts. Together with Frank H. J. Figge²⁰ we have shown that the hypophysis of the animal to be injected may be removed without decreasing, in any degree, the response to the thyroid-stimulating property of the extracts. We are not informed as to a possible adrenotropic component in our extract as the amphibians are not suitable material for such a test. The extract contains, however, some materials which produce, independently of the activity of the thyroid gland, both exophthalmos and a certain degree of tissue dehydration, as observed by Figge and Uhlenhuth²⁰ in thyroidectomized animals injected with the extract.

(b) *Effects of TA on Thyroid Structure* as shown by S. S. Schwartzbach, Guy P. Thompson, and Karl Mech (see references 3, 4, 6, p. 595, 9 and 26)

(1) TA, when injected intraperitoneally, reproduces exactly the structure which had been previously found characteristic of the active (releasing) thyroid.

(2) The colloid is released (see below), the follicles collapse and the lumina become slit-like^{6, 26}

(3) The cells are enormously increased in height and in size generally.

(4) Intracellular secretion vacuoles are present and may replace almost completely the cytoplasm (see references 6, fig. 95, 22, 26).

(5) Colloid vacuoles appear in large numbers.

(6) In addition, more recently it was found that the Golgi apparatus increases greatly in mass at first and later on breaks up into small particles^{17, 22}

(7) And further, that after prolonged injections the unstainable intracellular vacuoles are replaced more and more by deeply staining secretion droplets²²

In figure 6 are shown the more general changes of the thyroid structure as they appear in histological sections. Comparing a normal control (figure 6a) with the thyroid after six TA injections (figure 6b), the swelling and liquefaction of the cells are apparent. After 14 TA injections the almost complete absence of colloid may be seen (figure 6c), and after 22 injections (figure 6d) the presence of numerous droplets in the cells is evident.

In figure 7 is illustrated the vacuolization and liquefaction of the cells as seen in the fresh thyroid of TA injected animals. By the technic of examining the fresh thyroid of the salamander in the moist chamber and with oil immersion, only two days are required to determine whether or not the extract is effective.

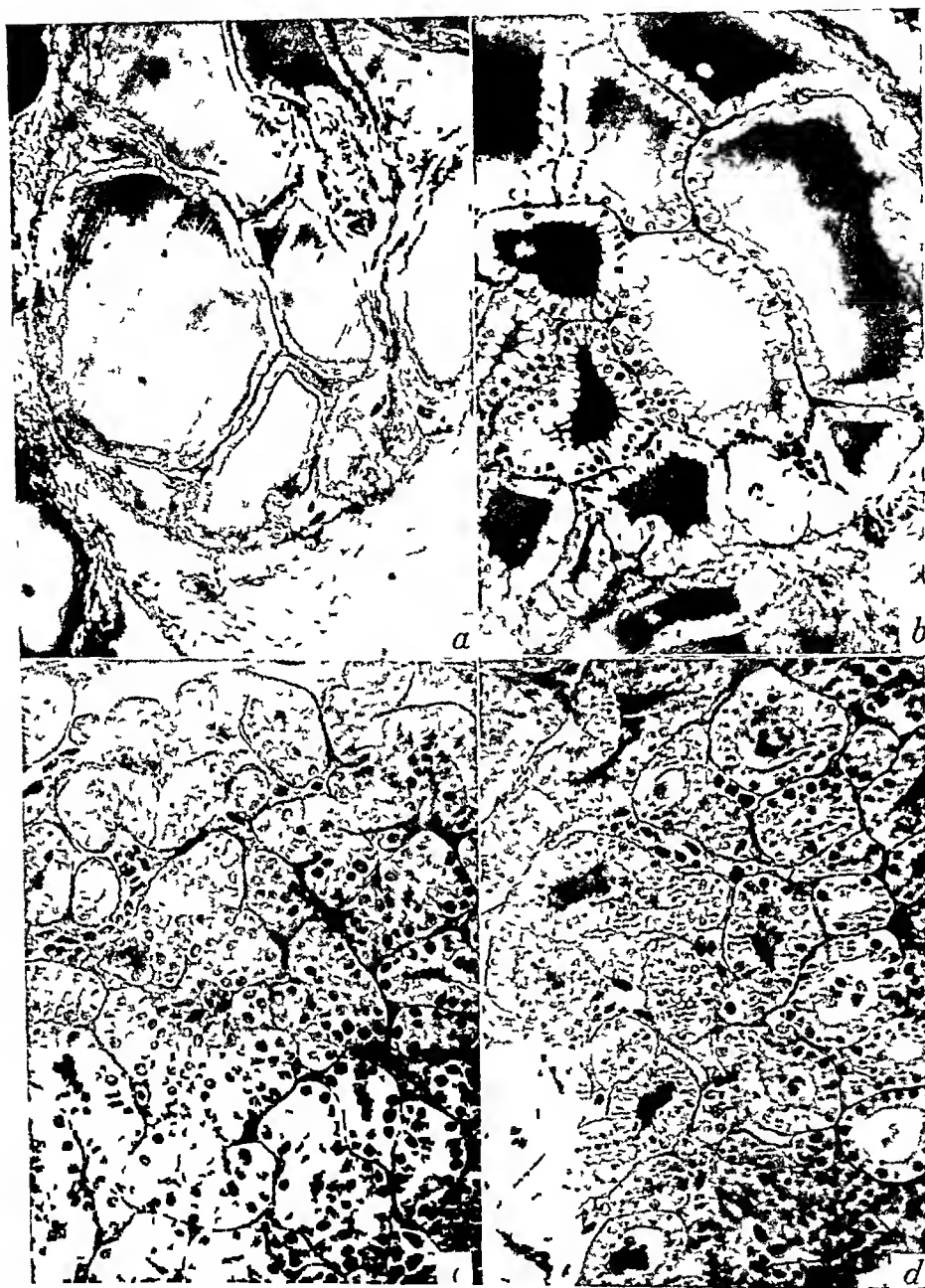


FIG 6 Gross histological appearance of thyroid activated by TA (a) Normal control Follicles large, epithelium flat, cytoplasm without secretion vacuoles (b) After 6 TA injections Follicles beginning to collapse, cells greatly enlarged, cytoplasm largely replaced by intracellular secretion vacuoles (c) After 14 TA injections, nearly complete release of colloid (d) After 22 TA injections, cells filled with deeply stained "Colloid droplet"

In figure 8 are shown the cytological changes taking place in the thyroid cells of adult animals after continued TA injections, as seen in microscopical sections In figure 8a are illustrated the cells of a normal, resting thyroid, the cells are filled with very small granules each of them contained within

a vacuole. These granules can be seen in the fresh thyroid and can be stained vitally, in the living animal, with neutral red, for this reason we called them NR-granules. In the fresh gland they move slowly about within

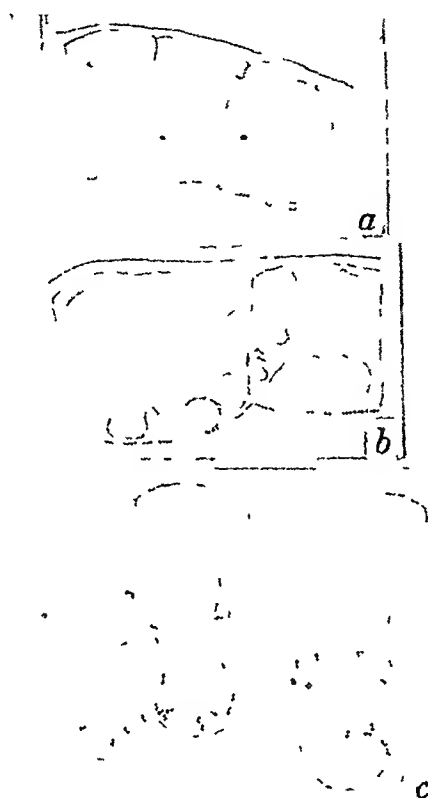


FIG 7 Cells of larval thyroid activated by TA injections as seen in the fresh gland under high magnifications (a) Normal control, neutral red granules numerous, but no secretion vacuoles (b) Activated gland, neutral red granules absent, but many large secretion vacuoles present (c) Activated gland, entire apical region vacuolized (From Uhlenhuth, Schwartzbach and Thompson, *Endokrinologie*, 1935, xvi, 9-19, figure 1)

the vacuole, a movement different from Brownian movement. In addition to the NR-granules, few small deeply staining droplets are present, likewise contained within vacuoles, in most of the dormant glands, however, droplets are absent.

In successful microscopical sections the NR-granules and the vacuoles containing them are of such excellent definition that they show perfectly well in photographs. In figure 9 is shown a follicle from a normal gland, it will be noticed that nearly the entire cell body consists of nothing but these small vacuoles containing each one granule. Owing to this peculiarity the protoplasm appears honeycombed or foamlike, a structure claimed long ago by Butschli as characteristic for all protoplasm.

Figure 8b shows the thyroid after six TA-injections, the cells have now greatly increased in size and the cell plasma is almost completely replaced

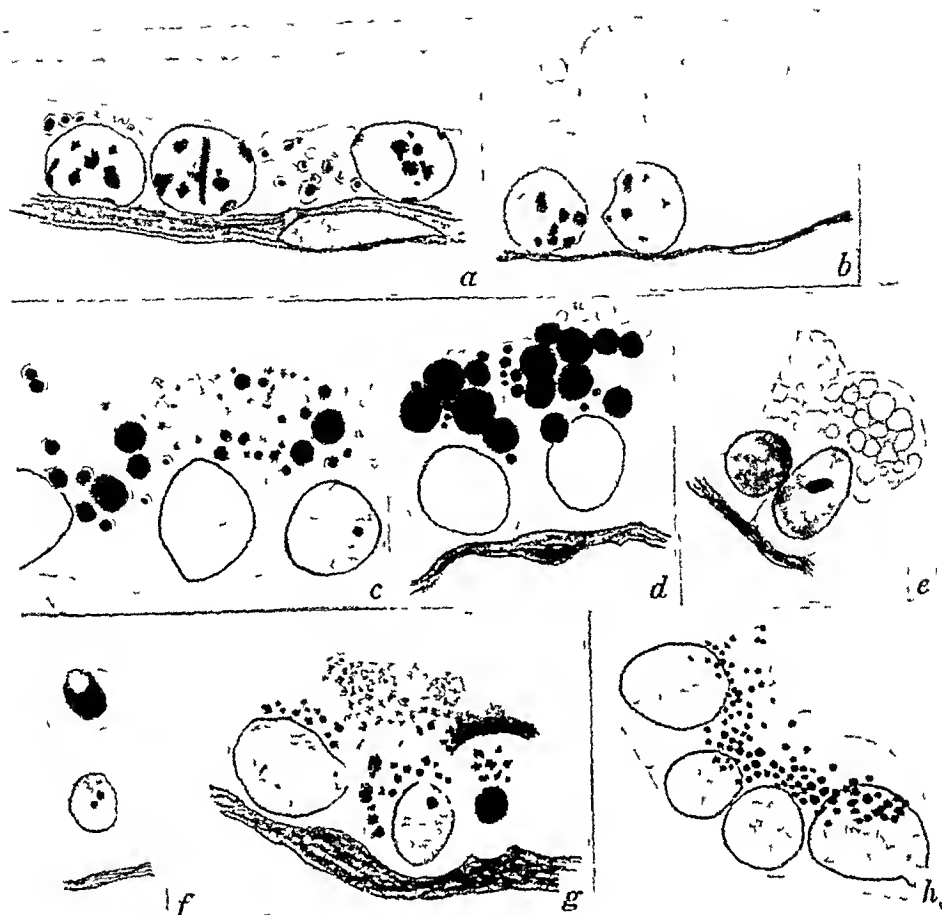


FIG 8 Cytology of adult thyroid activated by TA, as seen in histological sections
(a) Normal gland, (b-h) different phases of functional activity of thyroid cells

by large lacunae-like vacuoles. It will be noticed that the NR-granules have disappeared. In figure 8c is seen a thyroid after 15 TA-injections. The vacuoles have disappeared, while the NR-granules have reappeared. At the same time deeply stained colloid droplets have developed. These are of variable size and as they are contained each in a vacuole, the small droplets cannot be distinguished from the large NR-granules. As the number of injections increases, the number and size of intracellular droplets increase (figure 8d). Frequently cells are found now in which the droplets have dissolved into an unstainable fluid deposited in vacuoles (figure 8e). Under physiological conditions the colloid is excreted, by the cells, not in corpuscular form, but as a liquid, by a process of diffusion through the cell walls. Upon excessive stimulation, however, such as is effected by large numbers of TA-injections, colloid passes from the cells into the follicle lumen in corpuscular form, either droplets (figure 8f, partly liquefied droplet) are excreted or the whole apex (figure 8g), or even whole cells are shed. Especially this latter process results in degeneration and disintegration of large

numbers of cells. If TA-injections are discontinued the thyroid, after some time, returns to its normal condition. An arrangement of the granular content of the cell shown in figure 8*h*, with the granules occupying a position close to the nucleus, is a very characteristic stage of this reconstruction period.



FIG 9 Photograph of normal thyroid cells to show vacuoles containing "Neutral red granules"

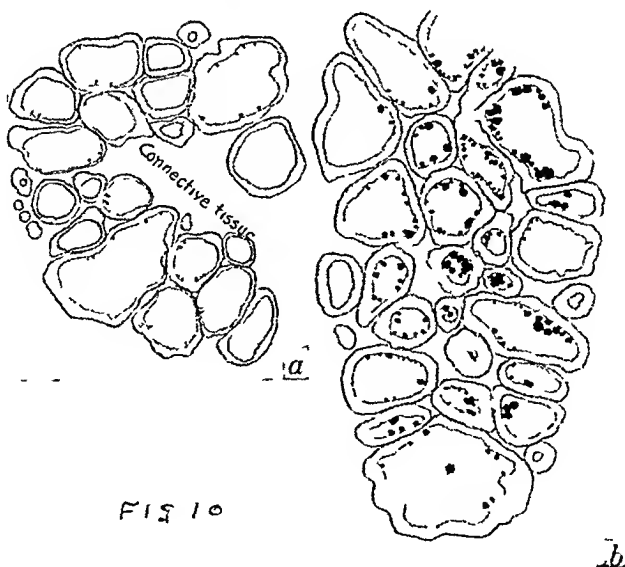


FIG 10 Showing the increase in size and number of colloid vacuoles (black dots) in the thyroid activated by TA (*b*) as compared to normal thyroid (*a*) (Taken from Figge and Uhlenhuth, *Physiological Zoology*, 1933, vi, 450-465, Plate I, figure d7)

The colloid vacuoles as seen after certain fixatives (Zenker) are illustrated in figure 10, in the gland activated by TA they are greatly increased in numbers as well as in size. The changes in the Golgi apparatus, effected by TA-injections will be evident from an inspection of figure 11

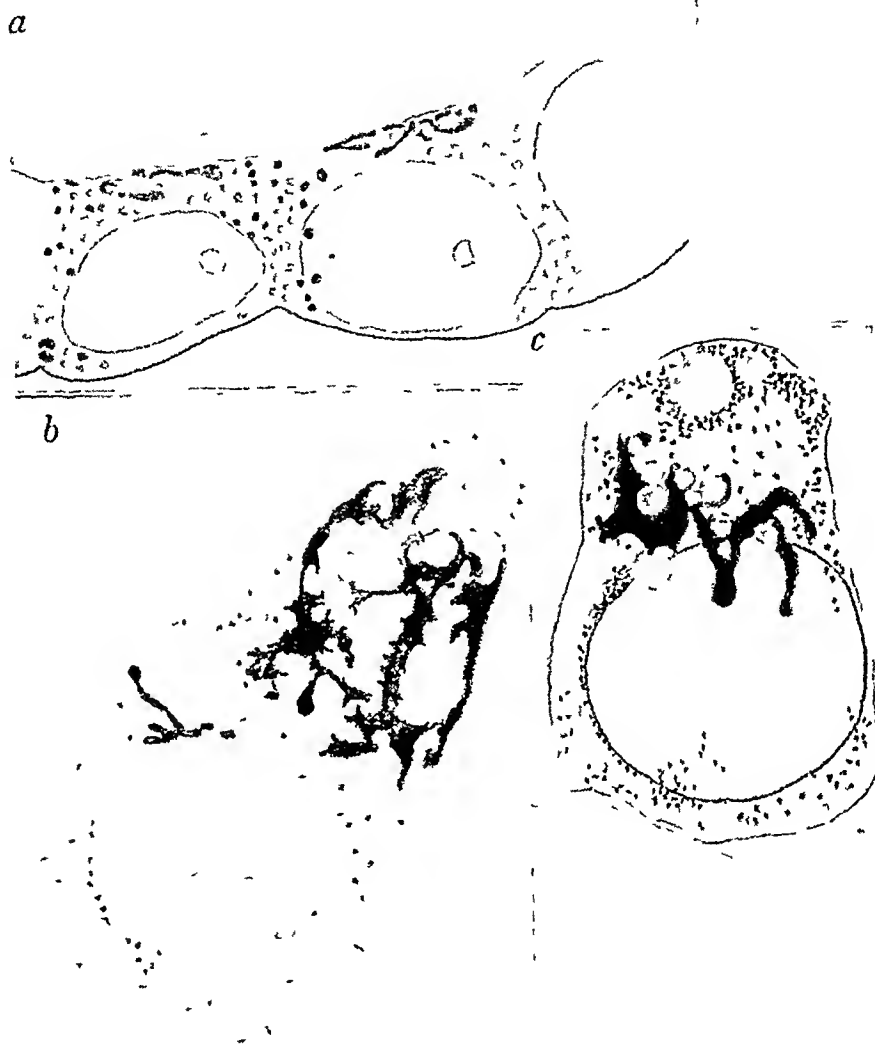


FIG 11 Showing the increase in size of Golgi apparatus in the cells of thyroid activated by TA (b and c) as compared to dormant thyroid (a) (From Quart Jr Microsc Sci, 1934, lxxvi, 615-646, figures 1, 22, 23)

(c) *Colloid Release as Effected by TA* Exactly as in spontaneous activation of the thyroid (see figures 1 and 2) so in experimental activation induced by TA-injections one of the most conspicuous processes is the release of the colloid from the lumen of the follicles. This effect was first noticed by Schwartzbach and Uhlenhuth in 1926 and was described in 1928⁶. Later on it was confirmed by Karl Mech and Eduard Uhlenhuth who devised

a technic by means of which an accurate measurement of the colloid content of the thyroid was made possible. In the following graphs the changes in the "colloid level" (i.e. amount of colloid expressed in percentages of total thyroid tissue) and in the cell height are indicated. It will be noticed that TA-injections are followed by an increase in the cell height and a decrease in the colloid level.

In figure 12, taken from the work of Thompson, Mech and Schenthal²⁸ is shown the effect of discontinuing the TA-injections. Four injections brought the colloid-level down to 8 per cent. After the fourth injection TA administration was stopped, immediately the colloid level began to rise. It is evident that the low colloid level which is the result of the colloid release

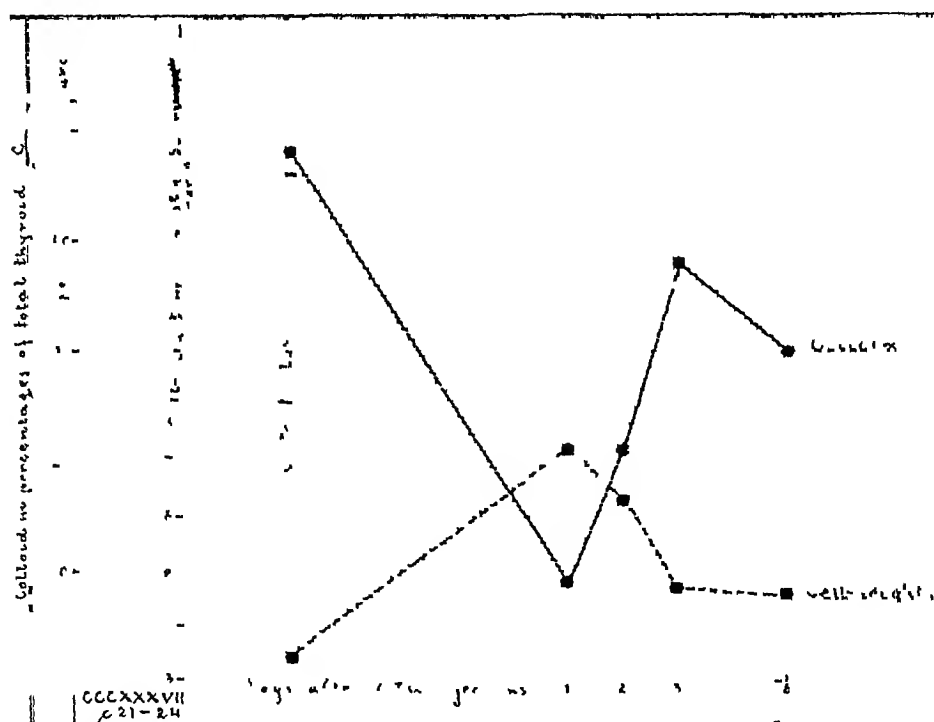


FIG 12 The drop of the black line indicates the colloid release effected by four TA injections. The rise of this line indicates that the follicles begin to refill as soon as TA-administration is discontinued. The dotted line indicates that the cell height is effected the reverse way. Note the striking agreement between the experimentally activated and the spontaneously activated (figures 2 and 3) thyroids (Karl F. Mech, Joseph E. Schenthal and E. Uhlenhuth).

effected previously by TA-injections, cannot be maintained after TA is discontinued. What happens when TA-injections are continued over a longer period is shown in figure 13 (taken from the work of J. Schenthal). At first the colloid level drops rapidly until after the sixth injection it reaches as low a value as can be obtained with the dose employed (50 mg AL per injection). After this value has been reached, continued injections maintain the colloid level permanently (over a period of three weeks) at this

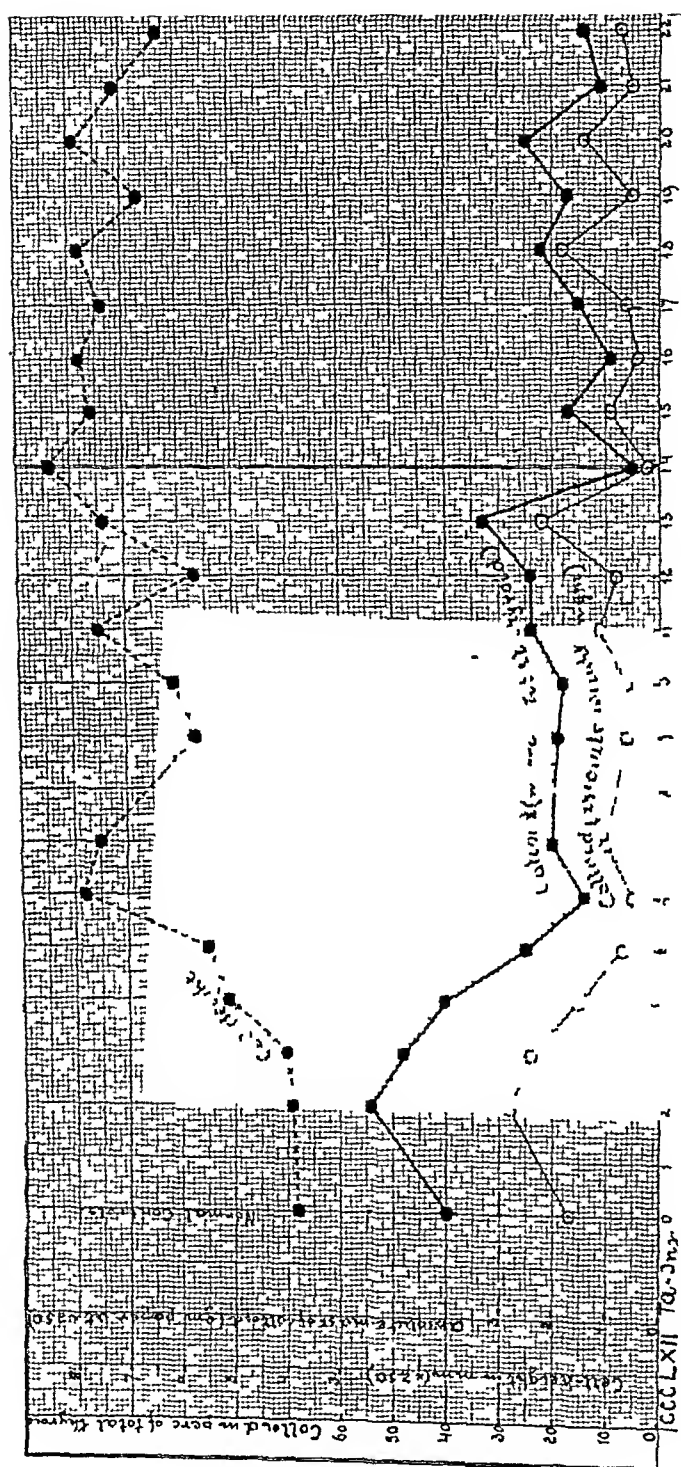


FIG 13 *Prolonged TA-injections in adult salamanders* The low colloid level is maintained and the increased cell height persists. Notice that (in the lowest of the three curves) the absolute weight of the colloid runs very nearly parallel to the colloid percentage, the decrease of colloid is so great and persistent, that even the individual variations in size of thyroids cannot mask it. (Joseph E. Schenck and E. Uhlenhuth)

value, but never permit it to rise to the value of the resting gland. Briefly, in our experiments, TA did not lose its efficacy of keeping the colloid level much below its normal value (i.e., at about 25 per cent of the normal colloid level). It will be noticed that the same relation holds true for the cell height which is maintained high throughout the experiment.

From this fact we concluded that at least in respect to colloid level and cell height, we have not felt the need of assuming the action of an "anti-thyreotropic hormone," reported by Collip in his work on warm-blooded animals.

(d) *Bodily Changes Resulting from TA-Injections* (1) We have already mentioned that in the larval aquatic salamander one of the most conspicuous effects of the thyroid hormone is the speedy transformation into an adult terrestrial animal. The same effect is obtained from TA-injections, owing to the release of the thyroid hormone, caused by TA.

(2) Loss of weight

(3) Severe exophthalmos

(e) *Effect of TA on Metabolism* (1) As thyroid hormone raises the metabolism, it was to be expected that TA, because of the release of colloid

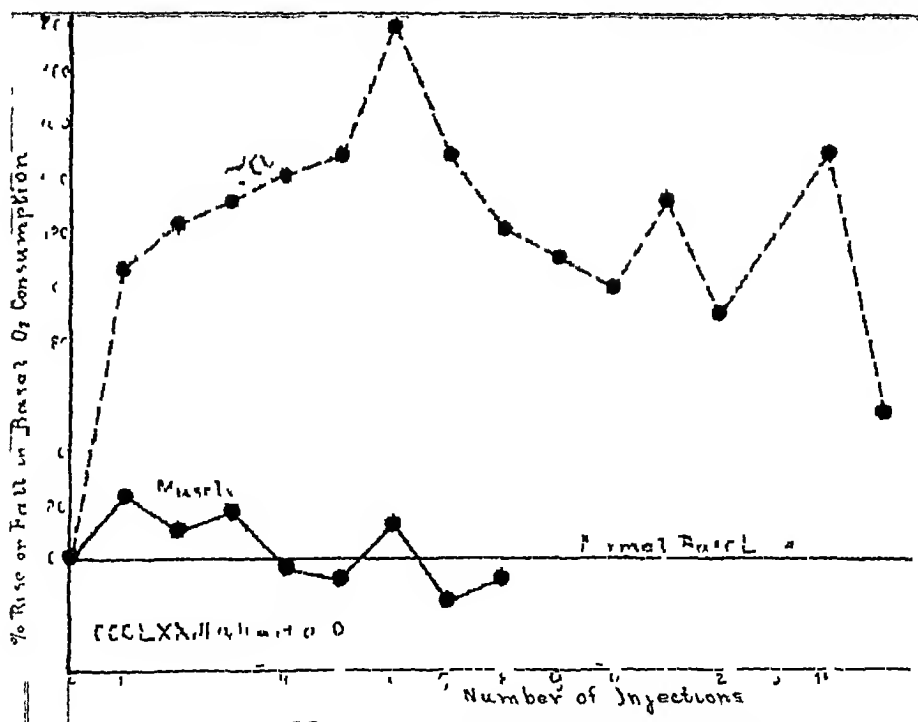


FIG 14 Thyreoactivator produces a 200 per cent rise in O_2 -consumption of the normal adult salamander (James U Thompson and E Uhlenhuth)

effected by it, would likewise raise the metabolism. Schwartzbach and Uhlenhuth^{11, 22, 27} found that in larval salamanders the basal metabolism rises from 30 to 115 per cent above the normal, if TA is injected.

(2) In the adult salamander, Thompson ^{4, 20} has shown, in an extensive series of experiments, that oxygen consumption increases up to 200 per cent above normal basal value, if daily injections of TA (equivalent to 50 mg AL) are made (figure 14). It will be observed from the graph in figure 14, that very much as in Collip's experiments on warm-blooded animals, a peak of oxygen consumption is reached after the sixth injection after which metabolism drops, a condition which has been explained by assuming the gradual development of an antithyretotropic hormone in an animal injected with TA over long periods. In the cold-blooded animal such an assumption is not necessary as the drop in oxygen consumption coincides with the time at which all the stored colloid which can be released at all with a given dose of TA, has been released. It is obvious that after this time the amount of colloid excreted into the blood circulation will be, at least, much smaller than the amount of colloid available before this time as the only colloid available from now on will be the colloid manufactured directly by the cells.

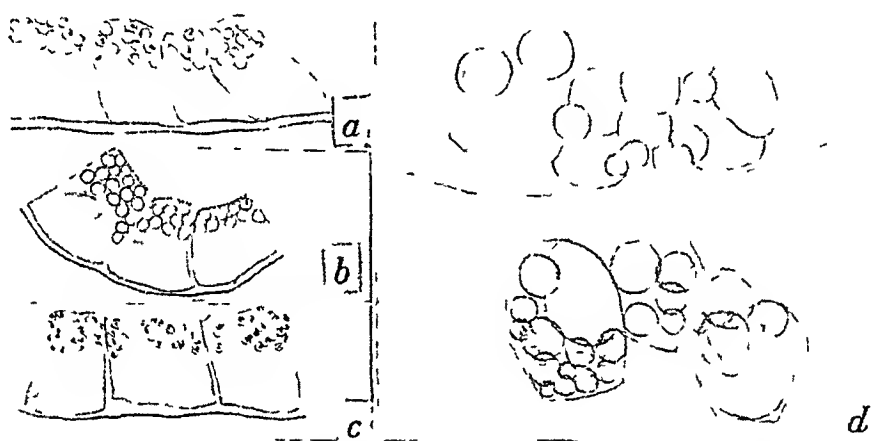


FIG 15 Injections of acid Ringer solution (b) and acid extract of posterior pituitary (c) (received 6 intraperitoneal injections of PL extracted from PL powder prepared under the supervision of Dr Frederick Fenger of Armour & Co) do not provoke the appearance of intracellular secretion vacuoles caused by TA-injections (d), no change as compared to normal control (a) (Guy P Thompson and E Uhlenhuth)

(f) *The Power of Activating the Thyroid Is Specific for TA* At first it was uncertain whether the property of activating the thyroid is specific for AL extracts. Large numbers of control experiments were required to test this point ^{3,4,7}. We obtained the following results:

(1) Neither neutral nor acidified Ringer is capable of effecting the changes of the thyroid gland which are obtained by TA-injections (see figures 15a, b, and d, illustrating experiments by Uhlenhuth and Guy P Thompson)

(2) Muscle extract has no effect on the thyroid

(3) Injections of posterior lobe extract are entirely inactive as shown

* The author wishes to express his thanks to Mr O G Harne, of the Department of Physiology of the University of Maryland for his valuable suggestions and assistance in selecting and constructing the apparatus used for the oxygen determinations

by Uhlenhuth and Thompson, figure 15 shows that in the adult animal the structure of the thyroid after posterior lobe injections (figure 15c) is the same as that of a normal control (figure 15a) and entirely unlike that of the thyroid of TA-injected animals (figure 15d). As recently it had been reported that thyroid activation may be obtained by posterior pituitary, Harry A. Teitelbaum tested this substance again in large numbers of animals. Again no activation of the thyroid could be secured by extracts made from bovine posterior pituitary either in alkaline, acid or neutral extractives.

(4) Parathyroid extracts prepared exactly like A.L. extracts did not activate the thyroid, as shown by Schwartzbach and Uhlenhuth (figure 16b).

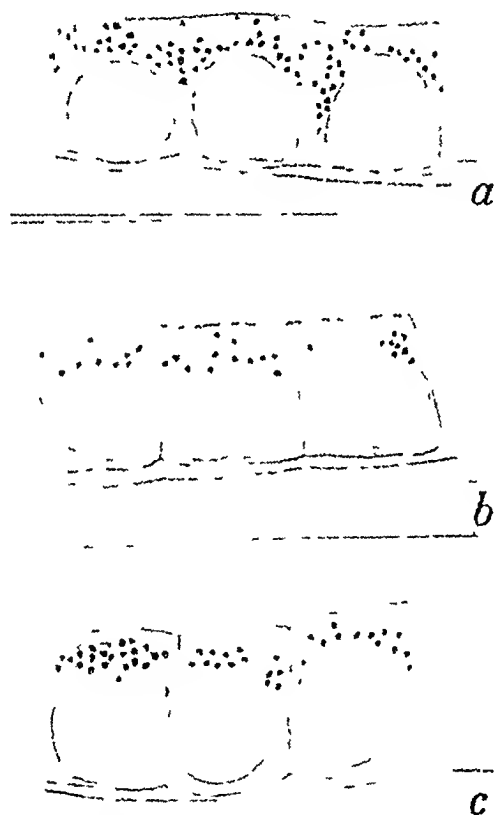


FIG. 16 (a) Normal control, Ringer-injected, (b) received 4 injections of acid extract of Armour's parathyroid powder, (c) received 3 injections of altogether 1 mg of adrenalin. Neither parathyroid nor adrenalin provokes the formation of secretion vacuoles characteristic of TA effect (Schwartzbach and Uhlenhuth).

(5) Adrenalin, a sympathicotonic substance, was administered to large numbers of animals. Although it produces many of the effects well-known from mammalian work, it does not activate the thyroid. This is illustrated in figure 16, from the work on larval salamanders by Schwartzbach and Uhlenhuth. Further data pertaining to this problem will be reported below.

(6) Pilocarpine, a drug which, among other actions, stimulates the parasympathetic nervous system, does not activate the thyroid gland, as shown in figure 17, from work on larval salamanders by Schwartzbach and Uhlenhuth

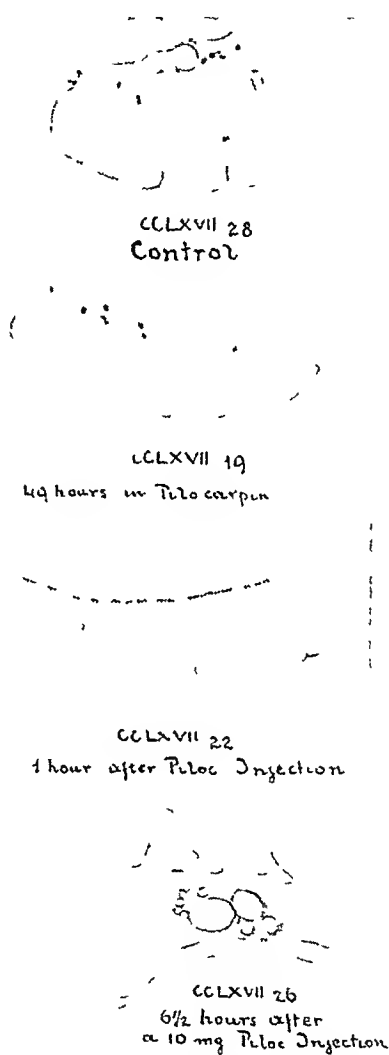


FIG 17 Neither immersion into pilocarpine nor pilocarpine injections produce any changes in the normal thyroid gland

(7) Thyroid substance leads to precocious metamorphosis in amphibians and, as in mammals, raises the metabolism of salamanders (shown by James U Thompson, in as yet unpublished work on adult salamanders), but it does not activate the thyroid. On the contrary it leaves the thyroid entirely dormant, as in the more advanced larval stages (figure 18), or even retards thyroid development, as in early larval stages (figure 19)

(8) Iodine affects the thyroid very profoundly, but it has no resemblance, in its action, to TA. At first it leads to pronounced enlargement

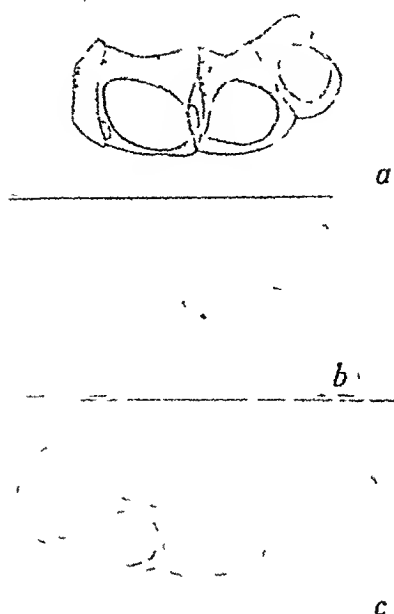


FIG 18 Effect of feeding thyroid-substance, upon the thyroid-cells, as demonstrated in the fresh thyroid of the tiger salamander by staining vitally the living animal with neutral red (a) Thyroid cells of normal control larva (b) Thyroid cells of a larva which has been under the influence of iodothyrene for 5 days (c) Thyroid cells of an animal which has been metamorphosed by a 12 days action of iodothyrene. Note that the thyroid cells of the animals treated with thyroid substance have failed to progress toward a more active condition, in particular intracellular vacuoles are absent



FIG 19 Effect of thyroid substance (iodothyrene) on larval salamanders, soon after hatching. It enforced metamorphosis before even the limbs were fully developed, but it did not activate the thyroid, nor speed up its development (a) Normal control early stage of thyroid (b) Thyroid after administration of thyroid-substance. Notice that the follicles are even smaller than in the control, and the cells have not yet attained the same orderly grouping into epithelial walls as they have in the controls

of the follicles and of the thyroid as a whole owing to increased colloid storage, much as it has been found by David Marine in the mammalian thyroid. Later on it brings about destruction of the thyroid cells and finally disintegration of whole follicles, followed by a decrease in the size of the thyroid and eventually by nearly complete disintegration of the organ^{15, 16} (figure 20)

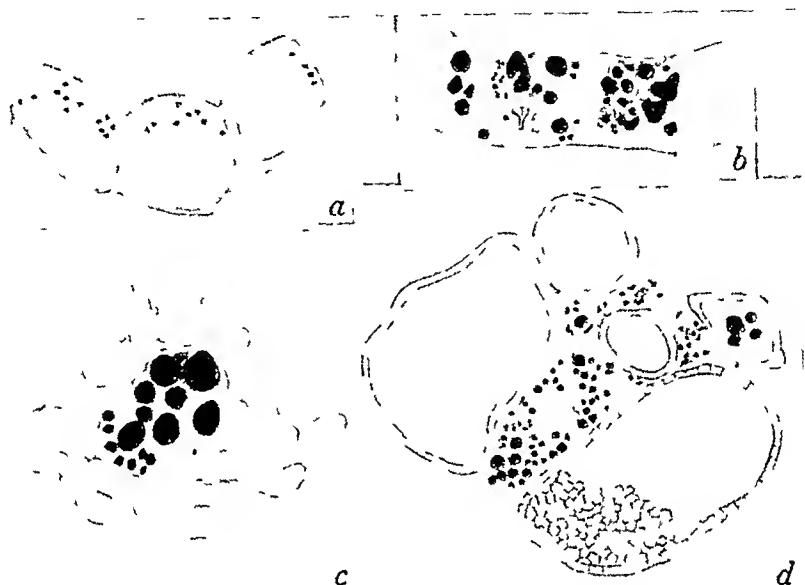


FIG 20 Destructive effects of inorganic iodine on thyroid cells as seen in salamander thyroids taken from animals stained intravitaly with neutral red and examined fresh (a) In the normal gland stainable substance contained in small, evenly distributed granules (b) Advanced lesions after iodine treatment, stainable substance beginning to fuse into lumps (c) Still farther progressed iodine lesions, whole areas in the wall of follicles begin to disintegrate (d) Finally whole follicles are destroyed and disintegrated (Redrawn from Uhlenhuth and Winter, Roux's Arch, 1929, cxix, 516-530)

(9) Thyroid substance produces its physiological effects no matter whether it is injected or fed. Much the same is true, in amphibians, for iodized proteins and amino-acids. Anterior pituitary, however, has no effects whatsoever when it is administered orally. It neither raises the metabolism (Schwartzbach and Uhlenhuth) nor does it change the structure of the thyroid gland (figure 21)

(g) *Physiological Inactivity of TA in the Absence of the Thyroid Gland* (1) After complete removal of the thyroid gland the physiological effects obtainable in normal salamanders by TA-injections cannot be reproduced, as shown by Schwartzbach and Uhlenhuth in 1928¹⁰. It was claimed by Spaul that he could obtain these effects even after thyroidectomy. Figge and Uhlenhuth, in carefully and completely thyroidectomized animals, repeated these experiments,^{19, 20} and confirmed the results obtained previously in collaboration with Schwartzbach.

(2) On the other hand, the presence of the pituitary is not necessary

for the production of these physiological effects after TA-injections. In experiments carried out by Frank H. J. Figge, it was shown that in the complete absence of the anterior, posterior and intermediate lobes of the pituitary, a perfect reproduction of the physiological as well as of the structural effects of TA is possible.²⁰

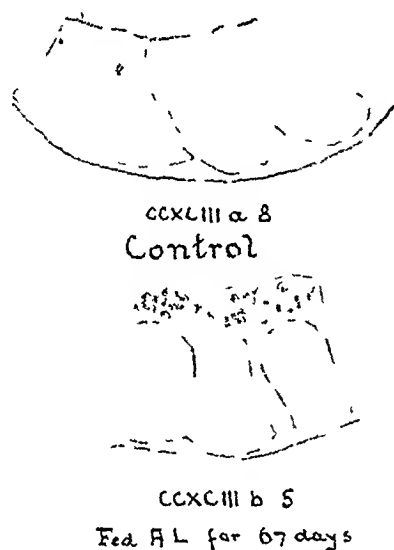


FIG 21 Oral administration of AL neither has any physiological effects nor does it activate the thyroid gland. Compare thyroid of AL-fed animal (b) with thyroid of normal control (a) (Schwartzbach and Uhlenhuth)

(h) *Conclusions and Confirmations* From all the data reported in this article the following conclusions were drawn (1928)

The anterior lobe of the pituitary manufactures a specific substance, the thyreoactivator, which alone among all the substances tested, is capable of activating, in a specific manner, the thyroid gland. By means of the thyreoactivator hormone, the anterior pituitary controls the activity of the thyroid gland.

The essential results submitted in this article were confirmed soon by other investigators and are now generally accepted. Thyreoactivator has been found to activate the thyroid of fishes (Collip), of amphibians (Houssay and collaborators in 1932), of birds (Schockaert 1930), and of mammals (Loeb and collaborators, 1929, Aaron, 1929, Houssay, in dogs, 1932, Collip, 1934).

III NERVOUS EXCITATION OF THYROID ACTIVITY

Experienced clinical observers, such as Buschan (1896), F. Chvostek (1917) etc., have placed much emphasis on cases of exophthalmic goiter which developed as a result either of continued grave nervous worries or of sudden severe nervous shocks. Owing to the discovery of the humoral

Figure 22

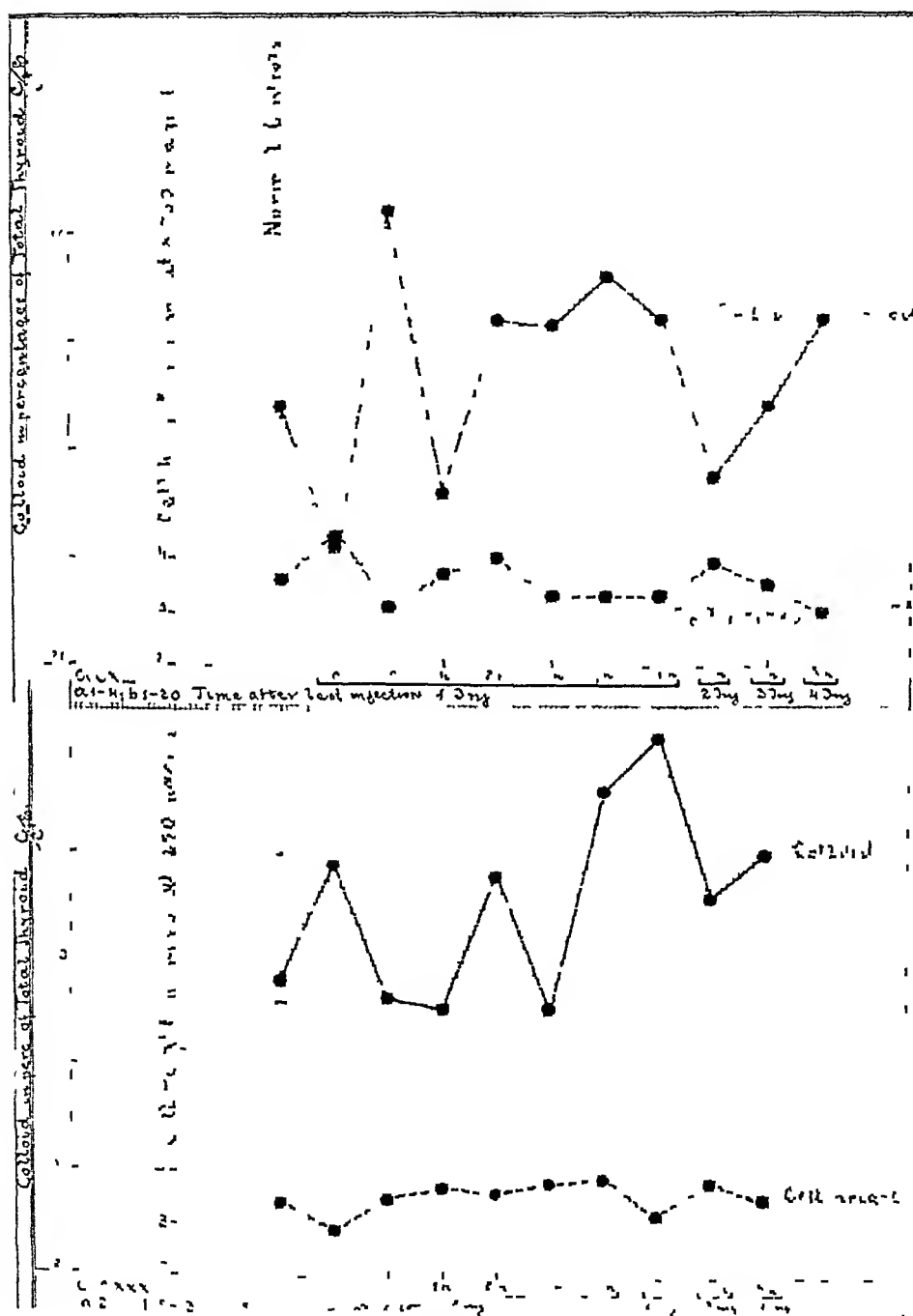


Figure 23

FIG 22 Adrenalin does not activate the salamander thyroid gland, it neither decreases the colloid content of the thyroid nor does it increase the cell height (Mech, Schenthal and Uhlenhuth)

FIG 23 Pilocarpine does not activate the thyroid gland of salamanders, it neither decreases the colloid content nor does it increase the height of the cells of the thyroid (Mech, Schenthal and Uhlenhuth)

excitation of the thyroid gland, interest in the nervous relations of the control of thyroid activity has suffered a setback. It is, however, especially the work of certain noted physiologists, such as Walter B Cannon and Leon Asher, which offers much encouragement to those who would search for some kind of nervous control, in addition to the humoral control of thyroid activity.

The discovery of the thyreoactivator has opened new roads to a successful attack on the question as to whether or not the nervous system plays any rôle in controlling thyroid activity. Our work along this line is based on the idea that, while stimulation of the nervous system may not activate the thyroid, it may make the gland more responsive to the exciting effects of

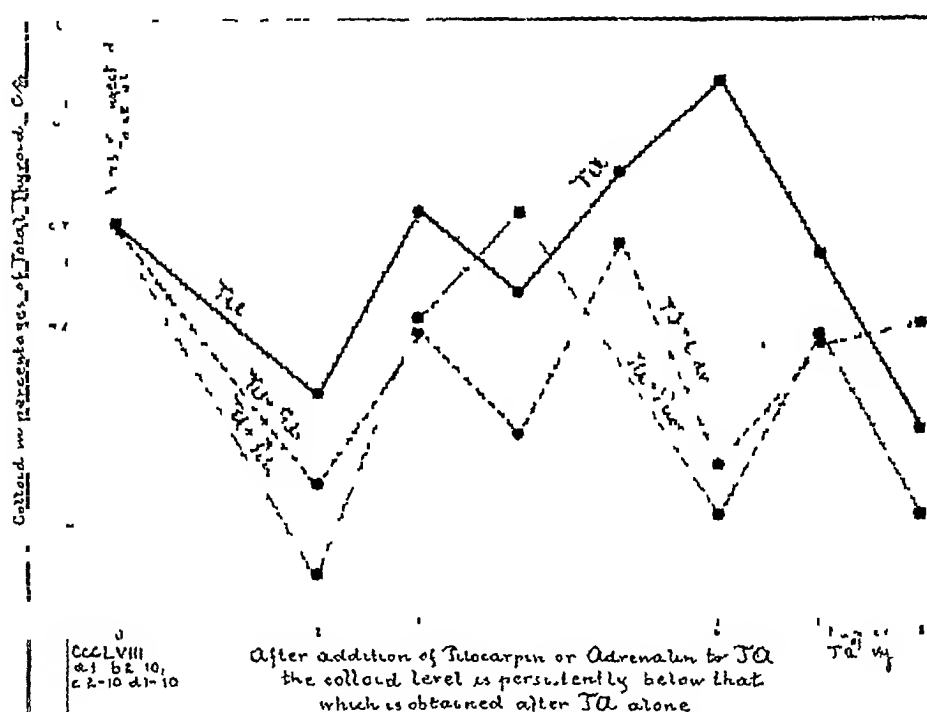


FIG 24 Adrenalin as well as pilocarpine when injected together with TA, increase the thyroid-activating power of the hormone in salamanders. The colloid content is distinctly more decreased when TA is injected with either adrenalin or pilocarpine than when TA is injected alone (Edgar van Slyke, James U Thompson and E Uhlenhuth)

thyreoactivator. Our results may be summarized under the following points:

(1) Intraperitoneal injections of adrenalin alone do not activate the adult resting thyroid, they neither decrease the colloid level nor do they increase the cell height in the adult resting thyroid (Mech and Schenthal, figure 22)

(2) Intraperitoneal injections of pilocarpine alone do not activate the adult resting thyroid of the salamander, they neither decrease the colloid

Figure 25

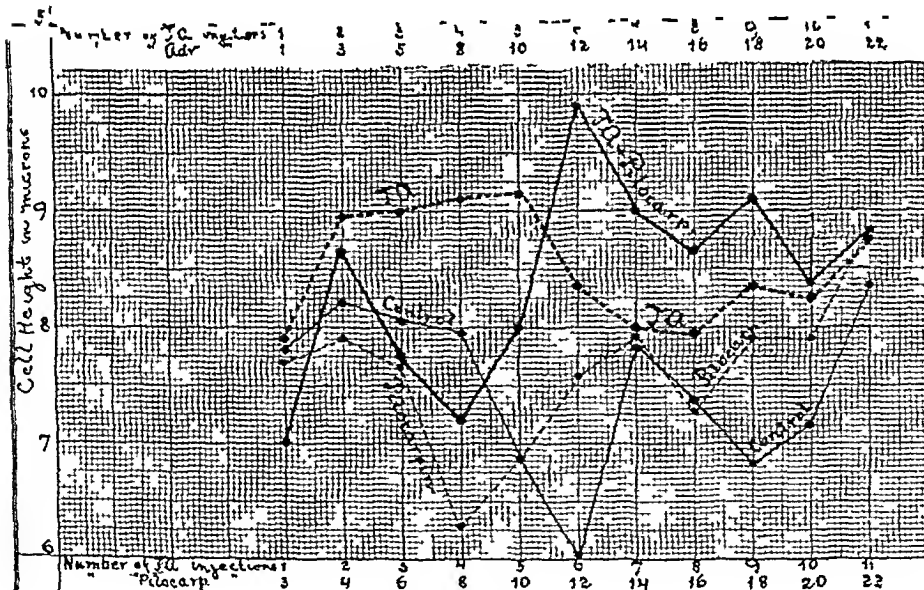
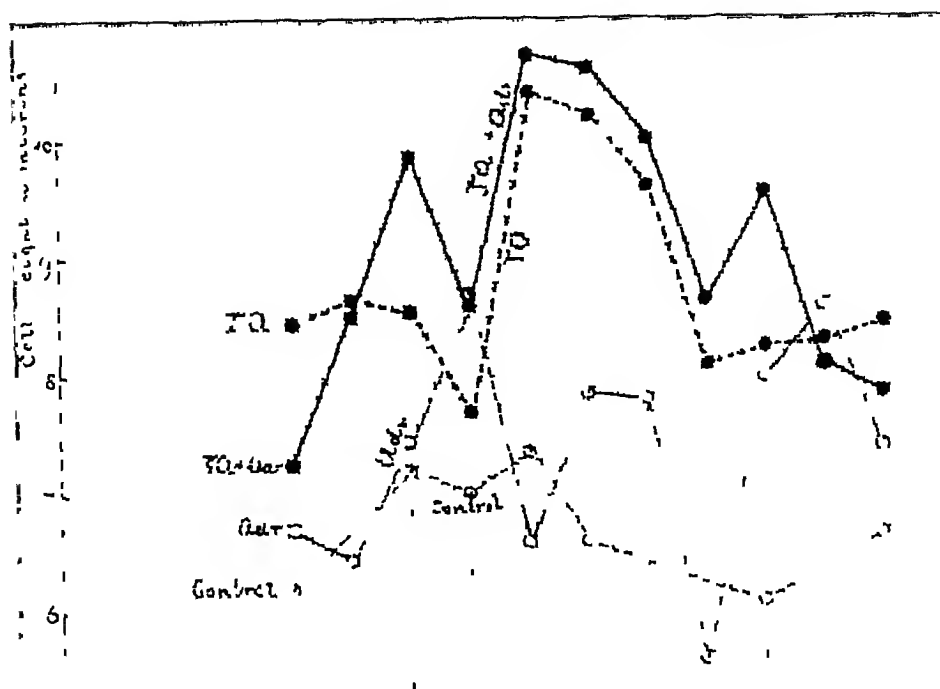


Figure 26

FIG 25 In the guinea pig TA combined with adrenalin produces a greater increase in cell height than TA alone, although adrenalin alone has no effect on the cell height of the thyroid (Teitelbaum and Uhlenhuth)

FIG 26 In the guinea pig although pilocarpine alone has no effect on cell height of the thyroid, TA combined with pilocarpine, after the fifth injection, produces a greater increase in cell height than TA alone (Teitelbaum and Uhlenhuth)

level nor do they increase the cell height (Mech and Schenthal, figure 23)

(3) Thyreoactivator injections, when combined either with injection of adrenalin or pilocarpine activates the adult resting gland of salamanders more effectively than thyreoactivator alone does, when either adrenalin or pilocarpine is added to TA the colloid level decreases more (figure 24), and the cell height increases more than when TA alone is injected, as shown by Uhlenhuth and Thompson ²⁴

(4) These experiments were repeated by Harry A. Teitelbaum ³⁰ in guinea pigs. Again it was found that adrenalin (figure 25) or pilocarpine (figure 26) alone has no effect on cell height. But when adrenalin is injected in combination with TA, the cell height is increased more than after TA alone (figure 25). When pilocarpine is injected in combination with TA (figure 26), it has at first a depressing action on TA effect, but from the sixth injection on, it accentuates the TA effect in raising the cell height. This as well as other differences between the amphibian and the mammal cannot be discussed here in detail, suffice it to mention that they are caused chiefly by differences in dosage and reaction to drugs in general.

(5) To test still further the accentuating effects which adrenalin and pilocarpine evidently have upon the power of TA in raising the activity of the thyroid, the amphibian metamorphosis was used as a method of assaying thyroid activity. It was found that in the presence of pilocarpine (dose 2 mg per injection) metamorphosis could be obtained with one-half the number (or less), and in the presence of adrenalin (dose 0.05 mg per injection) with two-thirds (or less) of the number of injections of TA that are necessary to obtain the same effect when TA alone is injected ²³. This result is exactly what would be expected if adrenalin and pilocarpine increase the responsiveness of the thyroid to TA.

(6) Conclusions. While we are not yet in a position to state that the effects we are getting from addition of adrenalin or pilocarpine to TA are caused by the nerve-stimulating properties of these drugs, we have learned that the activation of the thyroid by injections of TA is greatly increased when either adrenalin or pilocarpine is injected in combination with it.

IV SUMMARY AND CONCLUSIONS

(1) The anterior lobe of the pituitary manufactures and excretes a specific hormone, the thyreoactivator, which has the power of activating the thyroid gland (i.e., of causing, among other effects, release of the colloid). By means of this hormone the anterior pituitary is enabled to control thyroid activity.

(2) The effectiveness of the thyreoactivator can be greatly increased when either adrenalin or pilocarpine is injected in combination with it.

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AURICULAR FIBRILLATION, THE PRESENT STATUS WITH A REVIEW OF THE LITERATURE

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AURICULAR fibrillation is a disturbance in the action of the heart, in which the normal contraction of the auricles is replaced by irregular fibrillary twitchings in various parts of the auricular walls. The disorder is believed to arise from a disturbance in the mechanism of the cardiac impulse in which the wave of contraction, instead of following the normal path from the sinoatrial node down the conduction system, pursues a rapid, continuous and irregular course around the mouths of the great veins (circus movement). The resultant fibrillary twitchings, though incapable of causing an effective contraction of the auricles, set in motion innumerable impulses, estimated at four to six hundred per minute, of which only a portion can be transmitted to the ventricles by the conduction system. To this confusion of impulses the ventricles respond with a beat wholly irregular in both time and force and at a rate varying from 100 to 200 per minute (most commonly between 120 and 160), depending upon the integrity of the conducting tissue. Some of the beats are too weak to produce in the peripheral arteries a wave of sufficient magnitude to be perceptible to the palpating finger. The result is a "pulse deficit," the pulse rate at the radial artery being appreciably lower than the heart rate as counted at the apex.

Auricular fibrillation is one of the most important disorders of the cardiac rhythm, and is the commonest type of arrhythmia observed in decompensating hearts. At least 70 per cent of all cases of failure with congestion display this form of arrhythmia (Lewis¹). "Absolute arrhythmia" (*pulsus irregularis absolutus*), "irregular irregularity," and *delirium cordis* are synonyms indicating the essential clinical characteristics of the condition. The term "perpetual arrhythmia" (*pulsus irregularis perpetuus*), formerly used on account of the belief that fibrillation once established was permanent, now has been abandoned, since it is known that many patients frequently suffer repeated attacks which terminate spontaneously (paroxysmal fibrillation).

HISTORY

Although the existence of a condition characterized by an absolutely irregular pulse was known to clinicians for many years, it was not until 1903 that it was first described by Hering² as a distinct clinical entity. In 1906 Cushny and Edmunds³ described a patient with paroxysmal irregularity of the heart and suggested that the irregularity might be the clinical counterpart of auricular fibrillation which they had already observed in their laboratory animals. In 1909 this correlation was definitely established by Rothberger

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and Winterberg,⁴ and independently by Lewis⁵ In 1910 Fox⁶ and in the same year Mackenzie⁷ reported patients with auricular fibrillation in whom no structural defects of the heart could be detected, and in 1913, from clinical and pathological observations on a young subject (aged 23), Gossage and Hicks⁸ demonstrated fairly conclusively that this condition can occur in a heart which is normal apart from the fibrillation In 1914 Wenckebach⁹ reported the discovery by a patient that auricular fibrillation was favorably influenced by quinine, and in 1918 Frey¹⁰ showed that quinidine, the dextroisomer of quinine, is the more effective therapeutic agent in this condition In 1918-1920 Lewis, Feil, and Stroud,¹¹ and in 1921 Lewis, Drury and Ihescu¹² published their studies which tended to support the concept that the "circus movement" of a contraction wave was the physiological disturbance of the cardiac mechanism in clinical fibrillation This concept was based originally on the observations of earlier writers, especially those of Mines,¹³ Mayer,¹³ Garrey,¹³ and Levy¹³

ETIOLOGY

In the light of available information no definite etiological factor is recognizable in auricular fibrillation It is indeed known that auricular fibrillation is most often associated with certain types of heart disease, namely, rheumatic valvulitis, particularly mitral stenosis, and hypertensive heart disease It is also known that the arrhythmia occurs frequently in hyperthyroid states, with or without other evidence of heart disease However, less frequently auricular fibrillation has been observed in all other types of cardiac disorder, and in many instances where the heart, apart from the fibrillation, was apparently entirely normal It occurs at any age, though it is infrequent under the age of 20 years, and is very rare under the age of twelve The heaviest age incidence is in the third and fourth decades in the valvular group, and in the sixth and seventh decades in the non-valvular group The sex incidence does not appear to be particularly significant It has been found to vary widely in different groups of patients White¹⁴ noted about twice as many males as females showing the arrhythmia, while Cookson¹⁵ found twice as many females as males Evans¹⁶ in a comparatively small group of cases found a slight predominance of females in the rheumatic patients, and a ratio of three males to one female in the non-rheumatic group Brown¹⁷ in an analysis of 119 non-rheumatic cases showing auricular fibrillation which came to autopsy, found males predominated over females in a proportion of two to one However, of the 15 cases in this series which showed no cardiac pathology, 12 were females and three males In Friedlander and Levine's¹⁸ series of 35 cases of fibrillation without evidence of organic heart disease, there were 32 males and only three females

INCIDENCE OF ASSOCIATED HEART DISEASE

Of the various forms of cardiac disorder with which auricular fibrillation is apt to be associated, rheumatic heart disease represents the largest group. Evidence of this form of heart disease is found in more than 50 per cent of all cases of fibrillation. In a recent tabulation of 14 available reports, comprising a total of 2958 patients with auricular fibrillation, Evans¹⁶ found the incidence of rheumatic heart disease to vary from 20 to 69 per cent, or an average of about 49 per cent. In his own group of 39 patients, rheumatic heart disease occurred in 22, or 54 per cent.

Second in importance is the non-valvular or non-rheumatic type of heart disease occurring in relatively elderly people (Cookson¹⁵, Stroud, Laplace and Reisinger¹⁹, Levine²⁰). There is some disagreement as to the exact nature of the pathological process represented by this group. Levine²⁰ described it as "the condition called chronic myocarditis in middle-aged or elderly people in whom there is no important disease of the valves but rather some functional or structural damage to the musculature of the heart." Cookson¹⁵ found in this group "no constant associated conditions, except that of age." On the other hand, Brown¹⁷ in his series of 119 cases of this type found that hypertension was the etiological factor in 79.3 per cent of the cases with permanent fibrillation, and in 86.5 per cent of the cases with transient fibrillation. Both Cookson and Brown found coronary disease insignificant as an etiological factor in this arrhythmia. Parkinson and Campbell²¹ noted hypertension in 24 per cent and "myocardial disease" in 22.5 per cent of 200 cases of paroxysmal fibrillation. It is possible that some of their "myocardial" patients properly belong to the hypertensive group. Fourteen of those patients showed "gross enlargement of the heart or signs of congestive failure," without evidence of arterial disease or any other etiological factor to account for the enlargement or the congestive failure. It was pointed out by Bell and Clawson²² that a diagnosis of primary hypertension is justified "in a person suffering from chronic cardiac disease with low or normal pressure, if there is a demonstrable cardiac hypertrophy of the left ventricular type not associated with any disease known to cause hypertrophy." Yater²³ in a study of 145 cases of auricular fibrillation found hypertension a commonly associated condition in the non-rheumatic group. The weight of evidence, therefore, points to hypertension as the clinicopathologic disturbance most often found in the non-valvular type of heart disease associated with fibrillation. This is not an unexpected finding in view of the known importance of hypertensive disease in the causation of non-valvular heart disorders.

The frequent association of auricular fibrillation with thyrotoxicosis has been noted by many observers and is now quite generally recognized^{24, 25, 26, 27, 28}. In the 2958 cases of auricular fibrillation, which Evans¹⁶ collected from the literature, the occurrence of thyroid disease ranged between 0 and 44 per cent, with an average incidence of about 9 per cent. In the 200 cases

with paroxysmal fibrillation of Parkinson and Campbell,²¹ there were 28 cases or 14 per cent associated with goiter. Obviously the incidence of thyrotoxicosis in this arrhythmia varies with the geographical distribution of goiter.

The nature of the injury suffered by the heart in thyrotoxicosis remains obscure. The majority of opinion holds that no permanent cardiac damage results even though intense hyperthyroidism has existed over a considerable period of time. The whole subject has been comprehensively reviewed in a recent paper by Maher and Sittler.²⁰ In a series of 180 cases of their own these authors found that "congestive heart failure was not present in uncomplicated thyrotoxicosis. The presence of this phenomenon was associated with the coexistence of a structural lesion. Abnormal cardiac physiologic function as determined clinically or demonstrated objectively by the electrocardiogram, such as heart block (all types), damage to the ventricular conduction system and auricular fibrillation, appeared to be manifestations of primary organic heart disease modified by the element of thyrotoxicosis. The effect of thyrotoxicosis appeared to be that of a catalytic agent. The course of the organic heart disease progressed more rapidly when thyrotoxicosis was active. The thyrotoxicosis brought to the surface latent cardiovascular lesions, which resumed their latency on the successful termination of the thyroid toxemia."

The association of auricular fibrillation with syphilitic heart disease is very uncommon. In his own series of 39 cases with persistent fibrillation, Evans¹⁶ found no instance in which syphilis was present. In the 2958 cases collected from the literature, the incidence of syphilis was approximately 1.5 per cent. Parkinson and Campbell,²¹ in their series of 200 cases of paroxysmal fibrillation, found syphilitic aortitis in five instances or 2.5 per cent.

The association of angina pectoris with auricular fibrillation is likewise uncommon. Cookson¹⁵ found only five such cases in a series of 2000 patients with fibrillation. The extraordinary rarity with which angina pectoris is observed in auricular fibrillation tends to support the conclusion of Brown¹⁷ and of Cookson¹⁵ that coronary disease is not a significant etiological factor in this arrhythmia. However, the writer has observed frequently the transient occurrence of fibrillation during the early course of acute coronary thrombosis. This also has been noted by others (Levine³⁰).

The relationship between auricular fibrillation and subacute bacterial endocarditis is remarkable. Both conditions are common complications in rheumatic heart disease, but it is well known that they very rarely occur together. High grade mitral stenosis appears to favor the development of fibrillation, bacterial endocarditis is more apt to be engrafted upon a mildly affected mitral valve and upon a deformed aortic valve (Fulton and Levine³¹). In a series of 1200 cases of auricular fibrillation Cookson¹⁵ noted three instances (0.25 per cent) in which fibrillation and infective endo-

carditis were associated. Two of the patients came under observation with both conditions already present. In the third case fibrillation developed just before death. He could find "no example in the literature in which the infection has developed in a patient already under observation with auricular fibrillation."

THE OCCURRENCE OF AURICULAR FIBRILLATION IN AN OTHERWISE NORMAL HEART

Since the demonstration in 1913 by Gossage and Hicks⁸ that auricular fibrillation may occur in a heart which is entirely normal apart from the fibrillation, there have been numerous confirmations of this observation. In 1926 Levine²⁰ reported "several individuals with transient auricular fibrillation and one with the permanent form who, after the most thorough examination, showed no evidence of any disease whatever, the heart except for the arrhythmia seemed entirely normal."

Parkinson and Campbell²¹ (1930) found no evidence of heart disease in 30 (15 per cent) of 200 cases of paroxysmal fibrillation. In 12 (6 per cent) of these patients there were "infective" and "toxic" conditions that might have caused the arrhythmia, in the remaining 18 (9 per cent) there was no apparent cause.

Fowler and Baldrige³² (1930) reported 10 patients in whom auricular fibrillation was the only evidence of cardiac disease. Seven of these were of the paroxysmal, and three of the persistent variety. In one of these patients the "fibrillation was attributed to the removal of cerumen from the external auditory canal, one to exertion, four to alcohol, one to carbon monoxide, one to ether and nitrous oxide anesthesia, and two were in attendance at gasoline stations." One of the patients who fibrillated for two and one-half years, later came to necropsy and "the heart was regarded as grossly and microscopically normal." These authors also collected 35 similar cases from the literature. In the latter the "fibrillation was attributed to such stimuli as electric shock, diseases within the abdomen, emotion and effort, and intoxication by various chemical substances."

Friedlander and Levine¹⁸ (1934) reported 35 cases of auricular fibrillation without evidence of organic heart disease. Of these, 13 were classified as transient, and 22 as permanent. This number represents approximately 6 per cent of all patients with fibrillation seen by them over a period of 14 years. The inciting factors in this group in order of frequency were exertion, gastrointestinal disturbances, alcohol, and upper respiratory infections. In 20 patients there was no ascribable cause.

Organ, Wolff, and White³³ (1936) reported a similar series of 49 cases of auricular fibrillation without other signs of cardiac disease. This group likewise represents approximately 6 per cent of the total number of patients presenting this arrhythmia seen by them over a period of years. Only three of these cases were classified as permanent, and 46 were of the transient or

paroxysmal type Two of these cases which came to necropsy presented normal cardiac findings In many of the cases there were no definite etiological factors In some the onset of the arrhythmia appeared to "be related to pneumonia, malarial chill, pelvic abscess, alcohol, ether, burns, gall-bladder colic, vomiting, surgical operation, exertion, and emotion" In no instance, however, "when more than one paroxysm had occurred was the same etiologic factor responsible for all or even more than two paroxysms in the same person"

EFFECT OF DRUGS AND CHEMICALS ON THE INDUCTION OF AURICULAR FIBRILLATION

Drugs and chemicals as primary factors causing fibrillation cannot be considered of great importance Organ, Wolff, and White³³ collected from the literature instances in which the occurrence of fibrillation in normal hearts was attributed to epinephrine, digitalis, acetylsalicylic acid, ether, alcohol, tobacco, hydrogen sulphide, arsenic, carbon monoxide, and gasoline fumes These rare occurrences, however, rather than being regarded as illustrations of specific pharmacological action, may be more logically viewed either as isolated instances of drug idiosyncrasy, or as examples of the "trigger" mechanism suggested by Friedlander and Levine¹⁸ According to this concept the drug or chemical acts as a trigger upon a heart which, though structurally normal, is yet functionally so altered as to be subject to the sudden inception of auricular fibrillation upon coming in contact with some irritating or exciting agent The same mechanism is suggested by these authors as a possible explanation of the spontaneous occurrence of fibrillation in certain otherwise normal individuals In such cases "it is possible that an inherent susceptibility to functional nervous instability provides a fertile field for the propagation and persistence of aberrant stimuli whenever these people are subjected to a particular inciting factor, i e, emotional strain, acute febrile or toxic disorders the trigger may be related to the adrenal gland"

As secondary factors in initiating fibrillation in definite disease states, the rôle of certain drugs and chemicals appears more clearly established McEachern and Baker³⁴ have induced fibrillation by the administration of digitalis in nine patients with cardiovascular syphilis This is particularly significant in view of the rarity with which fibrillation is ordinarily observed in syphilitic heart disease Recently Tung³⁵ reported the appearance of transient auricular fibrillation in 15 patients in association with full or excessive digitalization, and the disappearance of the arrhythmia on the withdrawal of the drug Twelve of these patients presented gross evidence of heart disease Of the remaining three, one suffered from mitral valvular obstruction due to a myxoma of the left atrium, and in another there was severe toxemia from suppurative pneumococcal pleurisy The third pa-

tient was an elderly man (64 years of age) with a carcinoma of the esophagus, atelectasis of the left lung, and displacement of the heart to the left

Rosenblum, Hahn, and Levine³⁶ produced transient auricular fibrillation in hyperthyroid animals by the injection of doses of epinephrine too small to alter the cardiac rhythm of normal animals or those with hypothyroidism Nahum and Hoff³⁷ have converted a normal heart mechanism into auricular fibrillation by the administration of 0.75 mg of acetyl-B-methylcholine chloride per kilogram of body weight in four patients with hyperthyroidism, but were unable to induce such changes in normal persons with even larger doses of the drug They were also able to produce fibrillation by means of the drug in electrically shocked animals Since the principal action of acetyl-B-methylcholine chloride is vagus stimulation, these investigators conclude that the production of fibrillation in the above described instances was the effect of two distinct factors (1) a vagus factor (from the action of the drug), and (2) an exciting agent acting on the heart (thyroxine or electric shock), which they designate as the "E factor" In consideration of the above described observations Nahum and Hoff³⁷ seek to explain the mechanism of clinical fibrillation as involving the interplay of the same two factors The "E factor" is represented by the stretching of the auricular musculature as in mitral stenosis and in congestive failure, by the overactivity of the thyroid in thyrotoxicosis, and by functional nervous instability in some organically normal hearts In the presence of any of the above-named states ("E factors"), should overactivity of the vagus develop, or should the individual be abnormally vagosensitive, auricular fibrillation may result This theory is not incompatible with the "trigger" concept of Friedlander and Levine

From the above considerations it appears clear that no well defined factor is recognizable as the cause of auricular fibrillation It seems rather that the development of the arrhythmia is dependent upon the interplay of a number of circumstances which most often arise in the presence of grave heart disease especially in mitral stenosis and hypertension, and in certain toxic states particularly thyrotoxicosis These circumstances, however, may also arise in apparently healthy states and initiate the arrhythmia in individuals with otherwise normal hearts The latter group constitutes probably about 4 to 9 per cent of all cases of auricular fibrillation

PATHOLOGY

Yater²³ studied microscopically 29 hearts which had been the seat of fibrillation From these observations and from a comprehensive review of the literature, he came to the conclusion that there were no specific histologic lesions characteristic of this arrhythmia This is in agreement with the previously published observations of Frothingham,³⁸ and similar conclusions have been reached by Cookson,¹⁵ Lewis,¹ White,¹⁴ Brown,¹⁷ Stroud, Laplace and Reisinger,¹⁹ and Friedlander and Levine¹⁸ Indeed, this now appears to be the generally accepted view

TYPES AND FREQUENCY OF FIBRILLATION

Fibrillation is classified as (1) persistent, permanent, or established, and (2) as transient or paroxysmal. Both varieties may occur in any type of heart disease or in a heart which is otherwise normal. Furthermore, the transient variety may, after a number of paroxysms, become permanently established. However, mitral stenosis more often favors the establishment of persistent fibrillation, while the transient type is more often associated with the non-rheumatic group and with the otherwise normal heart. Comparatively few statistics which bear on the relative frequency of the two types are available. In White and Jones' ³⁹ series of 376 cases of fibrillation which included 30 patients without other evidence of heart disease, 309 (82.2 per cent) were classified as established, and 67 (17.8 per cent) as paroxysmal. In Kohn and Levine's ⁴⁰ group of 49 cases, including three cases in which no other heart disease was demonstrable, 46 were classified as permanent fibrillation, and three as transient. (It is not indicated whether the three transient cases were among those with structural heart changes or coincided with the three patients in whom no other evidence of heart disease was demonstrable.) In three small groups of cases including only patients with no other evidence of heart disease the relative frequency of the two types was

	Permanent	Paroxysmal	Total
Oigam, Wolff and White ³³	3	46	49
Friedlander and Levine ¹⁸	22	13	35
Fowler and Baldridge ³²	3	7	10

DURATION OF THE PAROXYSMS

In the series of 200 patients observed by Parkinson and Campbell, ²¹ 160 had paroxysms lasting less than two days. In these the duration of the paroxysms varied from one to 48 hours. In 20 cases the attacks lasted from two to four days, and in eight the paroxysms varied in duration between four and seven days. The remaining 12 patients had paroxysms lasting longer than seven days, some of these attacks continued as long as three weeks.

Oigam, Wolff and White, ³³ in their series of 49 patients, noted "great variation in the duration of paroxysms—from the shortest of a few minutes to the longest lasting one year." Usually, however, the paroxysm lasted "a few hours or days."

Friedlander and Levine ¹⁸ "arbitrarily" classified the arrhythmia as permanent if it lasted longer than seven days, because "it was assumed that any attack lasting more than a week would not be likely to cease spontaneously."

The above observations appear to justify the conclusion that in the large majority of cases of transient fibrillation (over 90 per cent) the paroxysms do not last longer than seven days, but that in very rare instances a paroxysm may continue for as long as one year and may then cease spontaneously.

SYMPTOMATOLOGY

Palpitation is the most common symptom. There may also be exhaustion, breathlessness, faintness, and giddiness. Pain is rarely a complaint. Orthopnea was the first symptom complained of by one patient observed by the author.⁴¹ The onset of the attack may not be accompanied by any particular disturbance, so that the patient may not be aware that the cardiac rhythm has changed. In rare instances the onset is very stormy, being accompanied by intense distress with symptoms of shock, and prostration. In most cases, however, the patients become aware of the sudden onset of palpitation and experience a varying amount of discomfort without complete disability.

DIAGNOSIS

The diagnosis rarely offers any appreciable difficulty. In most cases the existence of the arrhythmia can be diagnosed by means of the palpating finger and stethoscope or naked ear. Levine,²⁰ quoting Sir Thomas Lewis, gives the following rule: "Given a decompensated cardiac with a heart rate as counted at the apex of over a hundred and a radial pulse that is appreciably less (a pulse deficit of ten or more beats) if the rhythm seems grossly irregular and the pulse is irregular in both time and force the condition is auricular fibrillation nine times out of ten."

The arrhythmia resulting from very frequent, irregularly spaced extrasystoles occasionally constitutes a problem in differential diagnosis. In that condition, as in auricular fibrillation, short, quick beats are followed by compensatory long pauses. However, in fibrillation long pauses also occur frequently after strong beats, a phenomenon not seen in the extrasystolic arrhythmia. Any factor which accelerates the pulse rate (e.g. exercise or atropine) tends to increase the arrhythmia of fibrillation, and diminish the irregularity due to ectopic beats. Conversely, any agent which lowers the pulse rate tends to diminish the irregularity of fibrillation and to accentuate the arrhythmia resulting from extrasystoles. Finally, the diagnosis can be established beyond the possibility of a doubt by means of graphic methods. The disappearance of the auricular wave in the polygraphic tracings confirms the absence of auricular systole. In the electrocardiogram this condition is indicated either by a complete absence of P-waves, or by a succession of rapid, irregular, fundamental oscillations upon which, in turn, still more quivers are superimposed. The ventricular complexes are very irregularly spaced, but are otherwise normal in design except for such changes as may be due to associated disease involving either ventricle.

THE EFFECT OF AURICULAR FIBRILLATION ON CARDIAC FUNCTION

The effect of fibrillation on cardiac function varies greatly. In some instances, at least for a considerable time, little or no harm appears to result from the arrhythmia, especially if the heart action is maintained at a rea-

sonably slow rate, either by digitalis or by organic heart block without drugs (White¹⁴) Friedlander and Levine¹⁸ observed a patient who had never received medication and was known to have had persistent auricular fibrillation for 31 years without incapacitating him until five years prior to his death when he developed a left homonymous hemianopsia undoubtedly due to cerebral embolism Another of their patients "has remained well for years without medication although the rate is always rapid"

In other instances, grave disturbance in cardiac function may follow rapidly the onset of fibrillation, even if no structural changes of the heart can be demonstrated by all available clinical means Such a case was recently observed by the author⁴¹ A married woman, aged 43 years, with an excellent past history began to fibrillate without apparent cause After fibrillating for about three months without treatment she developed severe congestive failure There was generalized edema with signs of fluid in the serous cavities Rest and digitalization for one week reduced the heart rate from 160 to 85, produced extensive diuresis with a loss of 15 pounds in weight, and restored compensation to a considerable extent Roentgen-ray examination disclosed that the pleural and pericardial effusions had largely disappeared and the cardiac shadow was nearly normal The electrocardiogram showed that the auricles were still fibrillating but that the heart was otherwise normal except for slight changes due to digitalis A "test" dose of 3 grains (0.2 gram) of quinidine was administered When the patient was examined two hours later the heart rhythm was found to be normal Quinidine in half grain doses twice daily was continued for two days Thereafter all medication was stopped Within one month the patient resumed her normal mode of life At this writing, 15 months since the last dose of quinidine, the patient remains entirely well As nearly as can be determined by all the clinical means available, including roentgen-rays and electrocardiographic studies, her heart is entirely normal

The only example found in the literature resembling this significant history is that of Case 186 reported by Parkinson and Campbell²¹ These authors point out "how much disability may be produced by fibrillation, apart from any other diseases of the heart"

Between the two extremes just described are found the larger number of patients in whom the arrhythmia causes a degree of cardiac embarrassment which adds measurably to the distress already present in the organic cases, and produces a certain amount of breathlessness and palpitation in those persons whose hearts are otherwise normal On the other hand, as already pointed out, and for reasons not altogether clear, the presence of auricular fibrillation very greatly reduces the possibility of the development of subacute bacterial endocarditis, and to a considerable extent lessens the severity of the pain of angina pectoris (Cookson¹⁵)

It is generally accepted that auricular fibrillation predisposes to the formation of auricular thrombi (Kohn and Levine⁴⁰), but that notwithstanding this increased tendency to thrombus formation, embolism is no more com-

mon than when the rhythm is normal (Lewis,⁴² Cookson,¹⁵ Kohn and Levine⁴⁰) However, embolism does occur more frequently when after prolonged fibrillation the rhythm changes to normal Apparently the sudden onset of normal rhythm is an important factor in the production of emboli (Mackenzie,⁴³ Kohn and Levine⁴⁰)

PROGNOSIS

In patients with fibrillation without other evidence of heart disease the outlook is very favorable In their group of 49 cases, Organ, Wolff and White³³ found few cardiovascular changes, "rarely serious and in some instances wholly incidental to the presence of fibrillation Hyperthyroidism was an uncommon complication The mortality from auricular fibrillation or from cardiac disease was almost negligible" These conclusions are in agreement with those of Parkinson and Campbell²¹ and of Friedlander and Levine¹⁸ In striking contrast is the unfavorable prognosis held by fibrillators with organic heart disease The average duration of life in such groups observed by Stroud, Laplace and Reisinger¹⁹ and by Cookson¹⁵ was from two and one-half to seven years The shortest duration of life was noted in those patients with organic heart disease who began to fibrillate before they reached the age of 20 years Their average length of life after the onset of fibrillation was less than one year A comparison of the prognosis in the two chief etiological groups, the rheumatic and the non-rheumatic, revealed no significant difference (Stroud, Laplace and Reisinger¹⁹)

TREATMENT

In a recent paper on this subject Kohn and Levine⁴⁰ state "It is indeed questionable whether any form of therapy to restore the normal rhythm is indicated in this condition" This statement must be construed strictly as being applicable only to fibrillation associated with grave organic heart disease, especially rheumatic mitral stenosis, for it is in this type of case that the dangerous untoward effects of quinidine (embolism, collapse, and sudden death) are most apt to manifest themselves It may be stated, therefore, that in advanced organic heart disease with auricular fibrillation of long standing the best results are usually obtained by adequate digitalization, sufficient to maintain a reasonably slow rate (70 to 80 per minute) and to reduce the pulse deficit to a minimum In such instances it is probably undesirable to attempt to abolish the arrhythmia by means of quinidine, for the normal rhythm thus established is not likely to be permanent and the benefits derived therefrom are not sufficient to compensate for the risk involved in the use of the drug On the contrary, occasional cases of organic heart disease with congestive failure appear to derive some advantage from auricular fibrillation since the heart rate may be slowed to more efficient levels with digitalis and the response to that drug is often better than when the rhythm is normal It also has already been pointed out that auricular

fibrillation reduces very greatly the possibility of the development of sub-acute bacterial endocarditis and sometimes lessens the severity of the pain in angina pectoris

Notwithstanding these apparent advantages of auricular fibrillation there are many obvious disadvantages in the continuation of the abnormal rhythm. Perhaps the most important of these is the relationship of the arrhythmia to embolic accidents, for although, as noted above, it is held by some authorities (Lewis,⁴² Cookson¹⁵) that, except under quinidine therapy embolism is no more common in cases with auricular fibrillation than in similar cases with normal rhythm, it is generally accepted that this arrhythmia predisposes to the formation of auricular thrombi. It is also fair to assume that if the auricular fibrillation is terminated shortly after its inception the chances for the formation of such thrombi are greatly reduced. The conclusion therefore seems justified that whenever possible without too great risk, the attempt should be made to establish normal rhythm. In auricular fibrillation of short duration (less than six months) occurring in cases where the organic heart changes are not too far advanced, the dangers attending the use of quinidine are relatively less serious. Hence, in such cases quinidine preceded by digitalization may be used with probable benefit and comparative safety.

The use of quinidine is also worthy of trial in the more advanced cases of chronic heart disease with severe decompensation which fail to respond to digitalis or any other form of treatment. Cases of this type have been reported (Van Nuys⁴⁰, Kohn and Levine⁴⁰) in which quinidine used as a last resort established normal rhythm and restored compensation.

In cases of auricular fibrillation without other evidence of heart disease, quinidine is the most effective therapeutic agent and is the therapy of choice. In such cases dangerous toxic effects from the drug are seldom encountered and the chances of success are further increased by preliminary digitalization (Sollman⁴⁷). After such preparation, a test dose of 0.2 gram of quinidine is administered. In some instances this single "test" dose is sufficient to restore a normal rhythm^{40,41}. If, however, the arrhythmia continues and no untoward effects from the test dose develop in six to twelve hours, the administration of the drug is resumed in doses of 0.3 to 0.4 gram at four to six hour intervals until normal rhythm is restored or until the appearance of toxic symptoms necessitates the discontinuance of the drug. After the restoration of the normal rhythm, a daily maintenance dose of 0.2 to 0.4 gram or more may be required to prevent recurrence of the arrhythmia. Often the rhythm will remain regular even if the drug is stopped abruptly after the cessation of fibrillation. In this type of case quinidine is almost invariably successful in restoring normal rhythm, and the patient often remains well indefinitely without further treatment.

The total amount of quinidine required to restore normal rhythm varies greatly. As already noted, a single dose of 0.2 gram may be sufficient

In some instances, however, very large doses up to three or four grams per day may be required (Lewis¹) Kohn and Levine⁴⁰ found no constant ratio between the duration of the arrhythmia, the clinical condition of the patient, and the amount of quinidine necessary to produce a normal rhythm. They found 0.2 gram of quinidine sufficient in one patient with moderate cardiac enlargement and congestive failure, in whom fibrillation was known to have existed for two and one-half months. In another patient, whose arrhythmia was of but a few days' duration, 10.5 grams of the drug were necessary before the rhythm became regular.

In thyrotoxicosis, auricular fibrillation may require no special treatment, since the adequate management of the primary cause often will result in a spontaneous cessation of the arrhythmia. If, in the absence of organic heart disease, such desired results fail to develop within one to three weeks after thyroidectomy, quinidine therapy will usually restore normal rhythm. A resumption of fibrillation after such restoration of regular rhythm usually signifies either that an insufficient amount of the gland was removed, or that some other additional cause was responsible for the arrhythmia.

In hyperthyroidism with normal rhythm, the important indication is the control of the thyrotoxicosis. The early use of iodine, glucose and surgery will tend to prevent the appearance of auricular fibrillation. It is questionable whether quinidine should be used prophylactically in such instances. Statistics bearing on this point are not now available.

The paroxysmal type of auricular fibrillation often requires no special treatment. As already noted, in about 80 per cent of the cases the paroxysms cease spontaneously in less than two days, in many the attacks last but a few minutes to a few hours, and only in very rare instances does a typical attack continue longer than one week (Parkinson and Campbell²¹). In paroxysms of relatively long duration treatment is indicated in accordance with the general principles already outlined. Quinidine in doses of 0.1 to 0.4 gram twice or three times daily may also be used prophylactically in cases subject to frequently recurring attacks.

Auricular fibrillation associated with a slow apical rate not the result of treatment is quite rare and usually signifies the presence of organic heart block. In such cases no special therapy is required apart from the measures indicated by the underlying cardiac condition. However, in the very rare instances where the auricular fibrillation and slow rate are associated with an otherwise normal heart, an attempt should be made to abolish the arrhythmia with quinidine.

Congestive failure is usually significant of grave organic heart disease. However, as has been pointed out above, severe congestive failure may result from untreated auricular fibrillation apart from any other disease of the heart. In such a case quinidine preceded by digitalization may bring about complete and lasting recovery.⁴¹

UNTOWARD EFFECTS OF QUINIDINE

Kohn and Levine⁴⁰ list the following as the most frequent symptoms of quinidine intoxication "Nausea, vomiting, epigastric distress, diarrhea, headache, palpitation, tinnitus, fear, mental depression, flushing, sweating, syncope, and a feeling of apprehension" They quote Carr and Spoene-man⁴⁸ who consider a rise in the pulse rate to 130 as an indication for the withdrawal of quinidine, since such a rise in the rate points to vagal paresis. Skin manifestations such as scarlatiniform rashes and urticaria may occur. The occurrence of embolic phenomena has already been referred to. Sudden death other than of embolic origin is also occasionally observed, possibly due to respiratory paralysis⁴⁰ or to ventricular fibrillation.

TREATMENT OF QUINIDINE INTOXICATION

The milder symptoms of quinidine overdosage are relieved by the discontinuance of the medication, as the drug is rapidly eliminated by oxidation and excretion.⁴⁷ In cases of severe intoxication with symptoms of respiratory embarrassment, life may sometimes be saved by artificial respiration and the intravenous or intracardiac administration of large doses (15 grains) of caffeine sodiobenzoate.⁴⁰

COMPARATIVE EFFECTS OF QUINIDINE AND DIGITALIS UPON FIBRILLATION

In properly selected patients quinidine is effective in restoring normal rhythm or in preventing paroxysms in from 70 to 80 per cent of the cases. It is slightly more effective in younger patients (Organ, Wolff and White³³). This may be due to the fact that in the older age group, cardiovascular changes are more apt to exist without their being clinically detectable.

Digitalis is useful in slowing the pulse rate and may possibly diminish the frequency of transient attacks (Parkinson and Bedford⁴⁹). However, in established fibrillation, digitalis alone is not effective in restoring normal rhythm (Friedlander and Levine¹⁸).

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"SURGICAL SHOCK" FACTORS IN PNEUMONIA

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UNDERHILL and his associates^{1, 2, 3} did experiments at the time of the World War on the effects of the gases chlorine, phosgene and chlorpicrin. He showed that these lung irritants caused massive pulmonary edema with marked blood concentration. The total extent of this edema was not measured, but it was shown to be a protein-containing exudate. The average increase in blood concentration of four dogs which inhaled 41 to 50 parts per million of phosgene for one-half hour was 166 per cent of the control value as measured by hemoglobin readings. Underhill⁴ showed that in the influenzal pneumonia that occurred during the War, a similar pulmonary edema with resultant blood concentration was one of the chief lethal factors. He showed that fluid introduction might be of aid in this condition and that by following blood concentration changes, prognostication was greatly aided. In 11 cases with no complications, nine had a hemoglobin percentage of over 120 with values going up to 140. Moon^{5, 6} also noted red counts of 6,000,000 to 8,000,000 with correspondingly high hemoglobin percentages in influenzal pneumonia. He noted at autopsy that there was extreme capillary congestion of the pulmonary and gastrointestinal mucosa, that the lungs were wet and bloody and that frequently there was an effusion of reddish fluid into the serous cavities. Moon and Morgan⁷ produced pulmonary edema in dogs by injections of sodium glycocholate with increase in the red count and hemoglobin percentage (2,300,000 and 35 per cent increase respectively in one dog). All of these reports indicate that pulmonary edema may result from both exogenous and endogenous toxic factors.

Underhill³ analyzed the edematous lungs of animals resulting from inhalation of war gases and found that the water content per unit weight of tissue increased. Sunderman⁸ reported that in pneumonia the serum albumin decreased, the globulin increased and the total protein tended to remain within the normal or lower normal limits. Moon and Crawford⁹ reported a case of shock syndrome in mercuric chloride poisoning with death 37 hours after taking the poison. In this patient there were 1500 c c of blood tinged fluid in the peritoneal and pleural cavities. The lungs weighed 1800 gm after considerable fluid escaped from them. This means that in the lungs and three major cavities there was an exudation of about 3000 c c, which if essentially blood and plasma is of great significance.

STUDY OF CASES

Necropsy records of a series of patients dying with pneumonia at the University of Chicago Clinics were studied. Twenty-three such cases were

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used for the present report and the weight of the lungs and presence of pleural fluid noted. These cases represented deaths from lobar, broncho- and terminal pneumonia and in many instances the pneumonia was not the sole cause of death. In these cases the average excess lung weight (assuming normal lungs to weigh 600 gm) represented 2.45 per cent body weight. In several instances there was appreciable pleural fluid. This brought the total increase to 2.81 per cent body weight as shown in table 1. No chemical analyses were performed, but if this amount represents blood or blood plasma it is of considerable significance.

TABLE I

Increase in Lung Weight and Exudation of Pleural Fluid in Patients Dying with Pneumonia

Case No	Patient Wgt Kg	Duration Disease Days	Excess Lung Wgt Gm *	Excess Lung Wgt as % Body Weight	Pleural Fluid Wgt Gm	Pleural Fluid as % Body Weight	Excess Lung Weight + Pleural Fluid as % Body Weight
1	68	2	1850	2.72	—	—	2.72
2	75	4	2230	2.97	—	—	2.97
3	73	7	2640	3.62	—	—	3.62
4	68	long	1200	1.77	—	—	1.77
5	74	short	1020	1.38	—	—	1.38
6	62	3	1290	2.08	—	—	2.08
7	71	9	2370	3.34	800	1.1	4.45
8	61	5	1490	2.44	500	0.8	3.26
9	62	8	2450	3.95	—	—	3.95
10†	64	10	1615	2.52	400	0.6	3.12
11	62	9	1890	3.05	1100	1.8	4.82
12	57	6	1700	2.98	100	0.2	3.16
13	47	7	1130	2.40	50	0.1	2.40
14	56	4	2000	3.57	75	0.1	3.70
15	53	6	1530	2.90	1000	1.9	4.77
16	68	—	1400	2.50	—	—	2.56
17	59	—	670	1.14	600	1.0	2.14
18	76	2	1340	1.76	—	—	1.76
19	68	—	1190	1.77	500	0.7	2.56
20	68	—	1010	1.49	50	0.1	1.56
21‡	72	2	1210	1.67	—	—	1.67
22	37	—	1300	1.89	—	—	1.89
23‡	45	8	1490	1.98	120	0.3	2.24
Average				2.43			2.81

* The excess of the lung weight over the arbitrary normal of 600 gm is tabulated in this column.

† Blood pressure 142 systolic six days before death.

‡ Blood pressure 130/70 eleven hours antemortem.

EXPERIMENTS

Since no lungs from human pneumonia patients were available for chemical analysis at the time this study was carried out, the lungs of two distemper and one pneumonia dog were analyzed and compared with those of a normal dog. Analyses of the entire lungs were performed and the

nitrogen and protein contents determined on selected portions of the liquid solution of digested lung as shown in table 2, rather than on small bits of solid lung. These analyses show that the nitrogen and protein content in the abnormal lungs is essentially the same as in the normal lungs, indicating that the pneumonic exudate was protein containing. For the sake of more conclusive results the lack of great increase in total weight of these lungs as compared to normal lungs is not helpful. However, in certain instances different portions of the lung (right or left side) were markedly edematous without corresponding dilution of the protein content.

TABLE II

Nitrogen and Protein Content of Normal and Inflammatory Lungs in Experimental Animals *

Dog No	Condition	Body Wgt Kg	Lung Wgt Gm	Lung Wgt as Per Cent Body Wgt	Lung	Lung Wgt Gm	Per Cent Nitrogen	Per Cent Protein
1	Normal control	6.8	132	1.9	Left	51	2.20	13.68
					Right	72	1.98	12.31
					Accessory lobe	9	2.57	16.06
					Average	—	2.25	14.01
2	Pneumonia	20.4	555	2.7	Left	400	1.71	10.68
					Right	115	2.26	14.11
					Accessory lobe	40	2.49	15.56
					Average	—	2.15	13.45
3	Distemper	10.4	147	1.5	Left	58	2.00	12.43
					Right	80	2.17	13.56
					Accessory lobe	9	2.84	17.75
					Average	—	2.34	14.58
4	Distemper	14.7	255	1.7	Left	95	1.92	12.00
					Right	75	1.77	11.00
					Accessory lobe	85	1.92	11.93
					Average	—	1.87	11.64

* These dogs were kindly donated for examination by Dr. O. H. Robertson

COMMENT

The amount of fluid lost in the various pneumonia cases is extensive, averaging 2.81 per cent body weight. The special significance of loss of this amount of fluid depends on the interval of time during which the loss occurs and on the composition of the fluid. As seen from table 1, death usually occurred several days after the onset of the disease. Since it is difficult to tell whether most of the fluid was lost over the entire course of the disease, or as a terminal phenomenon, the time factor is uncertain. Naturally the loss of considerable blood or fluid in a few hours is of much more serious

important than the loss of a similar amount of fluid over a period of several days. Likewise the composition of the fluid was not determined in any of our cases and only from analogous animal experiments was its plasma-like nature inferred. Furthermore, the presence of shock was not demonstrated in any of the 23 patients as few blood pressure readings were taken. Only two patients had blood pressure readings after entrance and none closer than 11 hours to the time of death.

This quantity of fluid when lost from the circulating blood stream can, however, be of lethal significance. Studies of the amount of plasma-like fluid lost in various other shock-like conditions, both clinical and experimental, indicate a loss of the following amounts: burns 3.2 per cent body weight (Blalock¹⁰), 2.2 per cent (Harkins¹¹), freezing 2.6 per cent (Harkins et al¹²), release of an extremity constrictor 3.5 per cent (Wilson and Roome¹³), bile peritonitis 2.5 per cent (Harkins et al¹⁴), intestinal manipulation 4.5 per cent (Blalock¹⁵), and plasmapheresis 2.6 per cent (Johnson and Blalock¹⁶), 4.0 per cent (Harkins and Harmon¹⁷). No attempt will be made at this time to demonstrate that the loss of this amount of plasma-like fluid was the cause of death in these particular conditions, but the comparison between these figures and the average loss of 2.81 per cent fluid into the lungs and pleural cavities of our patients is pertinent. While this average is at the borderline of the range of fluid loss serious in these other conditions, in several individual pneumonia patients the figure was much higher. To our knowledge little attention has been paid to the possible importance of this fluid loss in pneumonia.

CONCLUSIONS

In a series of 23 pneumonia patients there was a combined increase in weight of the lungs and exudation of pleural fluid amounting to 2.81 per cent body weight. Under certain conditions the loss of this much fluid from the circulating blood stream may be significant and a condition resembling surgical shock may possibly result.

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ENCEPHALITIS DUE TO UNDULANT FEVER, REPORT OF FOUR CASES¹

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It is a little more than 10 years since undulant fever was recognized in parts of the world remote from the Mediterranean basin. Since then cases have been reported from many parts of Europe, Asia, and this continent. In 1933, 1,787 cases were reported in the United States and it seems highly probable that this was but a small proportion of the true total incidence. Among the complications of the disease the occurrence of meningitis has been described. Hartley, Millice, and Jordan,¹ in 1934, reported a case of meningitis due to undulant fever in which the patient recovered. In their case, there was a prodromal period of four weeks which they suggested could have been due to encephalitis. Krabbe² reported a case of meningomyelitis due to Bang's disease but made no mention of a true encephalitis.

We wish to present four cases of encephalitis in one of which features highly suggestive of hypothalamic and pituitary damage were present. In all the cases, the agglutination test or skin test indicated that undulant fever was present and in all no other etiologic factor could be demonstrated. So far as we have been able to discover, this clinical manifestation of the disease has not been reported previously in the literature.[†]

CASE REPORTS

Case 1 The patient was a boy 14 years of age who had been well until four weeks before admission to the hospital. At that time he had an influenza-like infection and missed two weeks of school. When he returned to school, he felt much below par and did not take an active interest in school activities. The day before admission here, he complained that he could not see well and a severe headache developed.

Physical examination revealed a slight fever and marked choking of both optic discs with blindness in the right eye and very little vision in the left. The boy could not see well enough to permit study of the visual fields. Neurological examination and roentgenographic studies of the head revealed no other abnormalities. A lumbar puncture was done which showed an initial pressure of 190 mm of water with normal dynamics. Examination of the spinal fluid revealed findings which were not abnormal. The leukocyte count in the blood varied from 5,000 to 11,000 and the differential counts were normal.

Five days after admission, the patient complained of a generalized, severe headache and on that day he vomited. The fever continued to be present. Bilateral positive Babinski signs were present. An encephalogram revealed no abnormalities.

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[†] Since these cases were collected, we have been interested in three cases of undulant fever associated with papilledema reported by Rutherford³. He does not emphasize the presence of encephalitis as much as we have done, but we feel that all these cases fall into the same group.

The diagnosis at this time was encephalitis, but since the appearance of the optic discs indicated increased intracranial pressure, a right subtemporal decompression was done in an effort to restore the patient's vision. The decompression did not bulge postoperatively. The fever persisted, varying daily between 97.7° and 103° F and occasionally rose as high as 104° F. An agglutination test for undulant fever was done and was found to be positive in a dilution of 1:640.

Numbness of the legs and retention of urine developed, and in view of the previous findings the diagnosis was changed to encephalomyelitis. The vision began to return, the neurological signs began to diminish, and the patient was discharged on the twenty-ninth postoperative day. The temperature was 101° F.

Thirty days after his discharge from the hospital, the patient's temperature was normal but he was still weak. Two months later his vision had returned and he was free from symptoms and signs insofar as his original illness was concerned.

This boy, who lived on a farm, had consumed much raw milk, his father was found to have a positive undulant fever agglutination test.

Case 2 A woman 55 years of age was admitted to the Clinic in April 1934, complaining of "headaches and vomiting." Seven months before admission, fever and chills had been present for four weeks and no cause was found. Two months before admission, similar symptoms had been present for 10 days and at this time, headaches and vomiting began which did not stop. She was in a hospital elsewhere for one week and was in a stupor during that time. A lumbar puncture had showed no abnormalities.

The patient entered the hospital for observation. Roentgenographic studies of the head, chest, kidneys, ureters, and bladder revealed no abnormalities. No evidence of tuberculosis could be found by roentgen examination or culture from voided and bladder urine. There was a slight haziness of the optic discs but the visual fields showed no changes. Lumbar puncture revealed no abnormal findings. The initial spinal fluid pressure was 170 mm, and following removal of 6 cc of spinal fluid was 110 mm of water. The total protein was 20 mg and no globulin or cells were present. There was a suggestive bilateral digital reflex. It was noted that a slight fever was present while the patient was in the hospital. A diagnosis of mild encephalitis was made and she was allowed to go home.

The patient was readmitted for study and recheck 10 months later. The headaches were still present but less severe. The vomiting had ceased but there was some nausea, and the temperature rose to 100° F each day. Undulant fever agglutination tests were negative but an intradermal test using 0.1 cc of Brucellin was markedly positive, and with this test the temperature rose to 100.5° F. Culture from a duodenal drainage revealed diphtheroid bacilli and yeast but no organisms of undulant fever. The positive reaction of the intradermal test in our opinion established the diagnosis of chronic undulant fever as the only demonstrable cause of this patient's symptoms.

Case 3 The patient was a young married woman 25 years of age who entered the Clinic May 24, 1934, complaining of fatigue, gain in weight, and scanty menstruation which had been present for two years. The onset of her symptoms occurred one and one-half years before this examination with an acute illness which was characterized by fever and extreme exhaustion, and the patient had never been well since that time. Somnolence became a very bothersome symptom, she had difficulty in awakening before noon each day and her previously excellent memory had become poor. Exhaustion had been so severe that bed rest was necessary for one or two weeks at a time. No headaches, diplopia, polydipsia, or polyuria were present. Libido began to decrease slowly until sexual desire was completely gone. About 25 pounds in weight had been gained. Menstrual periods had begun at the age of nine but had been irregular until the age of 14 when they became regular.

A fairly normal pregnancy terminated eight months before our examination Six weeks after delivery, the periods began again but they had become more scanty each month until at the time of our examination, very scanty menstrual flow occurred for part of one day each month

Physical examination revealed a woman 61 5 inches tall who weighed 145 pounds The temperature and pulse rate were normal and the blood pressure was 98 mm systolic and 70 mm of mercury diastolic The distribution of body fat was of the cerebral type The optic discs were hazy but examination of the visual fields revealed them to be within normal limits No clinical signs of hypothyroidism were present Laboratory study revealed the urine to be normal as was the blood except for 45 per cent lymphocytosis Complete blood chemistry examination revealed no abnormalities except in the level of the cholesterol which was 231 mg per 100 c c A glucose tolerance test was done using 100 grams of glucose orally Blood sugar determinations fasting one-half, one, two, and three hours following glucose administrations were 88, 117, 105, 84, and 78 mg per 100 c c The basal metabolic rates averaged minus 12 per cent Roentgenograms of the head revealed no evidence of pathological change and dental roentgenograms revealed no evidence of infection

Bio-assays revealed a positive Friedman test which was probably due to antuitrin-S (pregnancy urine prolan) which had been administered until four days before admission Assay for urinary estrin by the Kurzrok method on a 24 hour specimen of urine showed 3 4 and 4 0 rat units on two examinations

Hypothalamic damage was indicated because of the rather marked weight gain which took place in the presence of fever, the fact that it was distributed as in pituitary or cerebral disease and because of the excessive somnolence which occurred Damage to the pituitary region was strongly suggested by the marked diminution in libido and by the occurrence of hypomenorrhea The metabolic rate and glucose tolerance were not decidedly abnormal but were consistent with some damage to these structures

A diagnosis of pituitary hypothalamic syndrome following encephalitis was made which corroborated the diagnoses not then known to have previously been made separately by Dr W James Gardner and Dr Louis J Karnosh

After 10 months, no improvement was found and Dr Frank J Geib suggested that the condition might be due to undulant fever The agglutination test was positive in a dilution of 1 60 and severe reactions occurred after the administration of undulant fever vaccine in amounts less than 0 5 c c Further investigation of the temperature showed that fever recurred at regular intervals For from 16 to 17 days, the patient would be free from fever, then for eight days fever would be present, only to disappear for about 16 days again The symptoms were all aggravated during the period of fever

With our knowledge of the preceding cases, we felt that it was logical to presume that undulant fever caused this patient's symptoms Undulant fever vaccine was administered and one year later the patient was somewhat improved, but some reaction still occurred after the use of the vaccine and fever recurred at regular intervals During the periods when the patient was free from fever, there was little local or general reaction to vaccine, but both local and general reactions increased during the febrile period

Case 4 The patient was an unmarried woman 31 years of age who complained of diplopia, headache, and staggering gait She had been well until eight years before this examination when menstrual irregularity developed which was associated with considerable excitability That year a partial oophorectomy was performed with no immediate change in the menstrual cycle Later, the periods slowly became more frequent and more prolonged It was not long after the operation until the patient had a "nervous breakdown" which lasted most of the year Fairly frequent attacks

of fever occurred and during these attacks she was confined to bed. Her symptoms then disappeared except for the menstrual irregularity.

Seven years after the onset of the first symptoms, the patient began to be extremely excitable again, and this was accompanied by persistent diplopia. The nervousness became so severe that she was confined to a sanatorium for five weeks but showed no improvement. Later, drowsiness progressed to coma and she was confined to the hospital for three weeks. The temperature varied from 105° to 107° F, and the neurologist in charge made a diagnosis of encephalitis. The patient was discharged from the hospital. At the time of discharge she weighed about 60 pounds. The coma and somnolence subsequently disappeared and her weight increased to 125 pounds.

One year later, in the summer of 1935, the patient again began to have severe headaches with marked persistent diplopia. The gait was staggering and there was distinct static ataxia. The diplopia was relieved with prisms but monthly examination of the visual fields showed a marked and progressive concentric diminution of the entire field. Undulant fever agglutination tests had given negative findings.

The patient reentered the hospital in December 1935. General physical examination revealed no abnormalities except those mentioned above. The basal metabolic rate was minus 11 per cent, the blood Wassermann was negative, the urine was free from sugar, albumin, pus, and casts with a daily output of approximately 2,000 c.c. The hemoglobin was 12.5 grams per 100 c.c. of blood, the red blood cells numbered 5,200,000, the leukocytes numbered 7,500 with 40 per cent lymphocytes. The daily temperature was about 99.4° F. Roentgen examination of skull and chest showed no abnormal changes. Lumbar puncture showed a spinal fluid pressure of 80 mm. of water with normal dynamics. The cell count was 4 with a negative Wassermann reaction.

An undulant fever skin test with 0.05 c.c. of undulant fever vaccine (Jensen-Salsbery) was markedly positive, producing an abscess after 72 hours. This sloughed, then healed after 10 days. Vaccine therapy was instituted with marked local and systemic reactions.

Diagnosis Chronic undulant fever encephalitis

DISCUSSION

The relationship between encephalitis and undulant fever first was suspected in the first case and this was proved insofar as was practicable. In the second case, the diagnosis of encephalitis was made 10 months before undulant fever was suspected as the etiological factor. In the third case, decreased menstrual flow was associated with somnolence and other evidence of hypothalamic damage.

Since we have depended to a rather large extent on a markedly positive intradermal test for the diagnosis in two of our cases and since this method has not been as widely used as the agglutination test, we wish to explain why we consider that such a diagnosis is warranted.

Cutaneous hypersensitiveness to *Brucella abortus* has generally been considered by those who have investigated it as a good criterion in the diagnosis of undulant fever. However, it need not necessarily be considered as evidence of active infection. From the work which has a direct bearing on this point, the following reports in the literature may be cited. In 1918, Fleischer and Meyer⁴ showed that infection of guinea pigs with *Bacillus abortus bovinus* always produces cutaneous hypersensitiveness. In 1929, Giordano⁵

reported that the intradermal injection of a suspension of killed *Brucella abortus* yielded unmistakably positive reactions in 25 known cases of undulant fever and gave negative results in 99 of 100 controls. Levine⁶ in 1931 reported the results of intradermal tests in 365 individuals. Using suspensions of *Brucella abortus* antigens, cutaneous hypersensitiveness was shown in 27 cases and in only four of these was there no history of undiagnosed illness.

Yeckel and Chapman⁷ in 1933 reported the results of 250 intradermal tests in which killed bacterial suspensions of *Brucella abortus* were used. Fourteen definitely positive reactions were obtained and in only one instance was there no history of possible undulant fever. These workers concluded that, in the presence of a negative agglutination reaction, the intradermal reaction may be positive and thus lead to a definite diagnosis. Goldstein⁸ found 26 positive cutaneous reactions to saline suspensions of *Brucella abortus* among 253 unselected cases in an area where undulant fever was prevalent, and 13 of these patients gave histories indicating possible sources of infection with *Brucella abortus*. Favorite and Curtis⁹ found positive skin tests in 10 known cases and only one positive reaction was obtained in testing 90 controls. A subsequent history in this one case was very suggestive and the patient was shown to have an agglutination titer of 1:250.

In our own series of 90 unselected cases in which a tentative clinical diagnosis of undulant fever had been made, the skin test was performed 55 times. In 29, the intradermal reaction was definitely positive despite negative agglutination tests.

We have seen two cases in which the skin test was negative, yet positive undulant fever agglutination was found in testing the sera. In neither was there a definite clinical diagnosis and there were other extenuating circumstances. In the first case, the agglutination titer was only 1:10 and autopsy showed the presence of miliary tuberculosis. In the second case, the agglutination test was positive in one laboratory but negative in another. Blood cultures and opsonic activity¹⁰ have not been determined in our cases.

In the intracutaneous tests reported here, with the exception of Case 2, 0.05 to 0.1 c.c. of Jensen-Salsbery undulant fever vaccine has been used. This contains a heat-killed suspension in normal saline of *Brucella melitensis*, variety *abortus* and *suis*, 50 per cent of each preserved with 0.5 per cent phenol. Each cubic centimeter contains six billion killed organisms. In Case 2 Brucellin was used. The Brucellin used in this test was made in Huddleston's laboratories where it was developed by Hershey. It is a soluble nucleo-protein fraction of the three species of *Brucella* in 1:1000 dilution in slightly alkaline physiological salt solution.

The area of redness resulting from such an injection may be from three to seven centimeters in diameter and occasionally larger. It is edematous, hot, and tender and at times lymphangitis, adenitis and fever may be present. In some cases, a necrotic core or abscess forms and, in many patients, healing takes place slowly, leaving an area of pigmentation which remains for

many weeks. Those intradermal reactions which disappear within two days may be considered to be of little significance.

In evaluating the significance of such a reaction, the history of the patient must be considered. In addition, it is frequently of significance that small doses of vaccine, which are given for therapeutic purposes, produce unusually great responses in temperature. Where other causes for fever and accompanying symptoms can be eliminated and, in the presence of a strongly positive intracutaneous reaction, we believe a diagnosis of undulant fever is warranted.

Two patients (Cases 1 and 2) have shown improvement without specific treatment. The third patient failed to improve without specific treatment but has shown some improvement since it has been instituted. While there is improvement at present in the condition of the fourth patient, her prognosis seems uncertain in view of the history. While the authors realize that the evidence presented above does not constitute proof that encephalitis in these cases was actually caused by growing undulant fever bacilli in the perivascular spaces or nervous tissue of the brain and cord, the findings are nevertheless highly suggestive that such was the case.

SUMMARY

- 1 Four cases of encephalitis have been presented.
- 2 The etiological factors have apparently been the organisms of undulant fever as determined by agglutination tests in two cases and by intracutaneous tests in the other cases.
- 3 In one of the cases, evidence suggestive of hypothalamic or pituitary damage was present.

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NONVALVULAR HEART DISEASE UNDER THE AGE OF FORTY-SIX YEARS ¹

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INTRODUCTION

NONVALVULAR heart disease, often misnamed "myocarditis," is generally regarded as a condition of degenerative nature in older patients, attributable to coronary sclerosis or hypertension or both. That it may be frequently found in youth is not well known, nor are the etiological factors behind it generally appreciated.

Because of the interest and obscurity of youthful nonvalvular heart disease, we have undertaken to review a large number of cases in the pathological records of the Massachusetts General and Boston City Hospitals, focusing our attention upon the myocardial lesions which were reported. We have limited the study to younger patients and so have arbitrarily excluded those cases over 45 years of age, in order to reduce the preponderance of coronary sclerosis and hypertensive heart disease that might mask other conditions. The more recent years were chosen because the necropsy records were more complete. The cases reviewed all came to autopsy between the years 1920 and 1933. In selecting the cases we have included all those with hearts showing no valvular deformities or congenital defects, but with muscle injury recent or healed, or increase in heart weight to 350 grams or more in women and to 375 or more in men. For children we accepted the figures given by Viëtor² and Muller³ as the normal range:

Birth	20 to 25 grams	2 years	45 to 55 grams
1 month	15 to 20 grams	4 years	65 to 75 grams
6 months	20 to 25 grams	8 years	95 to 105 grams
1 year	30 to 40 grams	12 to 16 years	150 to 250 grams

In the course of this study we have reviewed 4,531 cases in the records of the Massachusetts General (2,600) and Boston City Hospitals (1931). From this group 250 cases were selected which fulfilled the requirements stated above. The pathologic reports were studied with special reference to cardiac findings, although in many instances the description was limited to a routine gross examination. The work was supplemented by a survey of the clinical records of the cases selected from the pathological reports, with particular emphasis on such points as duration of the disease, degree of hypertension, anemia, and clinical and laboratory data. The material has been combined in the appended charts and will be discussed in detail under appropriate sections.

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Undoubtedly the most accurate way of estimating the weight of the normal heart is through the use of Smith's² coefficients 0.43 per cent of body weight for men and 0.40 per cent for women. However, since the weight of the patients was not regularly included in the clinical records, the method was not applicable in this instance. The limits of heart weight up to 350 grams for women and 375 grams for men, chosen at the advice of Dr. Tracy Mallory of the Pathological Department of the Massachusetts General Hospital, were placed somewhat higher than most estimates to compensate for the small amount of aorta (at the most 20 grams) which is included in weighing the heart.

In spite of the most careful examination of clinical records, it is impossible to exclude a past hypertension of which there is neither history nor evidence at the time of examination. In several of the cases selected the size of the heart seemed out of all proportion to any initiating cause that we could find. When the blood pressure readings consisted only of a single determination with the patient in congestive failure, it can hardly be said that hypertension had been excluded as a cause. However, the number of cases in which this probability existed was not very large, though the source of error must be taken into account in evaluating the results.

DETAILS OF THE PRESENT STUDY

Of the 4,531 necropsy records reviewed, 250 cases, or 5.5 per cent of the total number, were found to belong to the group which we have outlined. The pathological condition which was most commonly associated with myocardial abnormality was hypertension, frequently accompanied by nephritis, with acute and chronic infections a close second. The complete classification is given in table 1.

TABLE I

	Cases
1 Hypertension	97
(A) With nephritis	67
(a) Chronic nephritis	62
(b) Acute glomerulonephritis	5
(B) Without nephritis	14
(C) With other conditions	16
2 Acute and chronic infections	91
3 Blood disorders	27
4 Coronary occlusion	5
5 Congenital idiopathic hypertrophy	4
6 Hyperthyroidism	1
7 Cardiac failure of unknown etiology	8
8 Miscellaneous	17
Total	250

The highest incidence of these myocardial abnormalities was found in the group from 41 to 45 years of age, and the lowest from 11 to 15 years of age. Starting with a fairly high incidence in the first five years of life, there was a steady decline in incidence until the fifteenth year, following which there was a gradual rise. This variation is perhaps explained by the

progressive decline in acute infections of childhood up to the fifteenth year, and by the steady increase in other forms of heart disease after that time. Males predominated almost in the ratio of two to one (162 to 88). The age incidence for both males and females is given in table 2.

TABLE II

Age group (years)	Number of males	Number of females	Total
0 to 5	16	5	21
6 to 10	7	4	11
11 to 15	1	3	4
16 to 20	8	6	14
21 to 25	9	9	18
26 to 30	14	9	23
31 to 35	19	12	31
36 to 40	32	17	49
41 to 45	56	23	79
Total	162	88	250

HYPERTENSION

That hypertension is followed by cardiac hypertrophy in the great majority of cases has been frequently observed. Paullin, Bowcock, and Wood,⁹ in studying the complications of hypertension, found that cardiac hypertrophy occurred in 66.4 per cent of cases. In many cases of unexplained cardiac enlargement at the time of death, study of the records will show that a previous hypertension has existed. In 50 such cases O'Hare, Calhoun and Altnow¹² found that hypertension of varying grades had been present on earlier examinations, although during the terminal cardiac failure the pressure had dropped to normal.

The exact mechanism of cardiac hypertrophy is uncertain. That increased muscular work alone is insufficient to cause hypertrophy of the heart is shown by the fact that Marathon runners usually have hearts which are normal in size or even undersized.^{7, 8} Eyster's^{1, 4} demonstration of progressive cardiac hypertrophy in dogs after a temporary obstruction to blood flow in the aorta indicates that stretching of the muscle fibers may be the initial injury to which the fibers react by becoming hypertrophied. Whether this mechanism is operating in all cases of cardiac hypertrophy is uncertain, although it appears to be a rational explanation. The surprising absence of cardiac hypertrophy in some cases of prolonged hypertension may thus be explained by the supposition that the load was applied so gradually that dilatation never took place.

(A) *Hypertension with Nephritis*—The organic lesion elsewhere in the body with which abnormalities of the heart muscle were most often associated in the present series was chronic nephritis. Of the total of 250 cases, 67 or 26.8 per cent were found at autopsy to have one of the forms of

chronic nephritis* The factor which was common to the great majority of the cases in this group was hypertension Every case except one had a systolic blood pressure of 140 or more at the time of entry to the hospital, the one exception to this was a child of ten who had a blood pressure of 132/70, a distinct elevation for a child of that age A systolic pressure of 200 or over was observed in 32 of the 67 cases, and a diastolic pressure of 100 or over was found in 57 cases The heart weights in this group were all definitely above normal, the highest being 900 grams, and the average of the 65 adults (16 years and above) was 499.7 grams Those with a systolic pressure of 200 or over had hearts averaging 537.6 grams There is evidently some correlation between the degree of hypertension and the amount of hypertrophy, although other factors such as the duration of the hypertension, anemia, or intercurrent infections must also be considered

Aside from hypertrophy there were very few changes in the gross appearance of the hearts in these cases One showed small, flat yellowish areas in the epicardium and extending into the myocardium, while another had a few "milk patches" on the left ventricle and the right auricle The microscopic appearance of the heart muscle was no more characteristic than the gross appearance Thirty-one hearts were said to be normal microscopically, while 12 were not so examined In the remaining 24 cases the microscopic changes varied from diffuse fibrosis to perivascular areas of fibrosis with or without cellular infiltration In cases of malignant hypertension focal necroses were frequently described Edema of the stroma, fragmentation of fibers, and increase in size of individual fibers were also noted

Electrocardiograms were taken in but 22 of the cases and in 12 of these left axis deviation was noted This agrees with the work of Ziskin¹⁰ who found no constant changes in the electrocardiograms of 100 patients with hypertension, although 44 showed left axis deviation Additional electrocardiographic changes in our group were inversion of the T-waves, low or high origin of the T-waves, and slurring of the QRS waves

(B) *Hypertension without Nephritis* Fourteen cases of hypertension in which the renal factor was negligible have been grouped under the heading, "Hypertensive Heart Disease without Nephritis"

Nothing beyond minor degrees of arteriosclerosis was found in the kidneys of the "purely hypertensive" cases Since this form of heart disease is found largely in middle aged and elderly persons, it is not surprising that all our cases were in the upper range of our age group, between 38 and 45 years of age In about half of the cases cardiac failure was the cause of death, while in the others cerebral hemorrhage or pulmonary embolism were the terminal events The average weight of the hearts for this group was 545 grams Grossly most of the hearts were hypertrophied and dilated, while microscopically generalized and patchy fibrosis was noted The most

* Because of the necessity of condensing the article the tables of the individual cases have been omitted

common electrocardiographic changes were left axis deviation and inversion of the T-waves

(C) *Hypertension with Other Complications* This rather heterogeneous group of 16 cases has been separated from the other sub-groups because a definite hypertension existed as a complicating factor. In six of the cases acute infections, which, as will be shown later, are sometimes accompanied by cardiac enlargement, were present in addition to the high blood pressure. The myocardium in these cases was normal except for minor grades of hypertrophy. Four cases showed extensive cardiac infarction as well as an elevated blood pressure. In addition to recent or healed infarction, the hearts exhibited marked hypertrophy with an average weight of 662.5 grams. Since both cardiac infarction and hypertension are capable of producing enlargement of the heart, the part played by each is impossible to estimate. In the other six cases, in addition to moderate elevation of blood pressure, the following diagnoses were recorded: pyonephrosis with uremia, chronic tubo-ovarian abscess, exophthalmic goiter, carcinoma of a bronchus with small metastatic nodules, lymphoblastoma, and cirrhosis of the liver. Myocardial changes, except for slight increase in weight, were insignificant except for the tumor nodules in the case of carcinoma of the bronchus and fatty infiltration in the last two cases mentioned above.

2 ACUTE AND CHRONIC INFECTIONS

In 91 of the 250 selected cases acute and chronic infections were the primary causes of death. It is very difficult properly to evaluate the part played by the infectious process, since in many of the instances the marked cardiac enlargement indicated that another factor must have been at work. Those in which hypertension was known to have existed as a complicating factor have already been segregated into a separate group (1C). For purposes of discussion it is convenient to divide the cases in the following groups:

(A) *Acute Pulmonary Infections* In all acute infections there is probably some toxic action on the heart, but in pneumonia there is the added factor of stasis in the pulmonary circuit and anoxemia. In 1915 Newburgh and Porter,¹⁹ after injecting pneumonic blood into normal dogs, noticed that there was an initial loss of effectiveness of the heart as evidenced by a decreased stroke volume and lessened area of contraction. They observed, however, that this toxic effect wore off after a short while and that the heart rapidly readjusted itself to the altered conditions. So long as general nourishment was maintained and the initial dose was not too great the myocardium was quite able to cope with the toxin. In addition to this toxic effect, which in debilitated subjects may be quite marked, there is the added factor of increased resistance in the pulmonary circuit. Stone²⁰ found dilatation of the right heart in 39.4 per cent of 89 cases of lobar pneumonia and in 36.6 per cent of 112 cases of bronchopneumonia, while microscopi-

cally there was evidence of inflammatory and degenerative change in 61.9 per cent of 21 cases of lobar pneumonia and in 25 per cent of eight cases of bronchopneumonia. The whole heart was usually involved.

There were 32 cases of acute pleuro-pulmonary infections in our series, 23 of lobar pneumonia with and without complications, eight of bronchopneumonia with and without complicating conditions, and one of acute empyema. In all of these except one, the heart weight was above the average. The average weight of the hearts of the 28 adults was 413 grams.

In the majority of cases the myocardium was reported either as normal or as moderately hypertrophied or dilated. Microscopic examination was either essentially negative or not done in 23 of the cases, while in the others diffuse fibrosis was noted in four, cellular infiltration in two, fatty infiltration in one, and areas of necrosis and abscess formation in two. Four other cases of acute pulmonary infections were included under "Hypertension with Other Complications" because of a coincident high blood pressure.

(B) *Chronic Pulmonary Infections*. It has long been noted that chronic pulmonary disease, if obstruction to the pulmonary circulation is sufficiently great, results in a definite pulmonary hypertension with attendant strain on the right heart. Among the more common etiological agents are chronic bronchitis and emphysema, bronchiectasis, extensive fibrocaceous tuberculosis, thoracic deformities, extensive infiltrating tumors of the lungs, and endarteritis of the pulmonary vessels (Ayerza's disease). As Moschowitz²⁶ pointed out, obstruction to the pulmonary circulation by pressure upon or occlusion of the smaller vessels produces a hypertension which tends to engorge and dilate the right ventricle with eventual right sided hypertrophy. The added factor of pulmonary arteriosclerosis, which follows prolonged pulmonary hypertension, may serve eventually perhaps to aggravate the condition. When the right ventricle fails, the tricuspid ring is dilated and the effects are transmitted to the systemic venous circulation.

Long-continued bronchial asthma, especially when accompanied by emphysema, has sometimes been regarded as a cause of severe strain on the right heart, but recently Alexander and others,²⁴ in 50 such cases, were unable to find any evidence of myocardial damage as the result of asthma alone. Pulmonary abscess, unless extremely extensive, does not alter the mechanics of the lesser circulation, though it may exert a deleterious effect on the heart as a whole because of the toxemia. Tuberculosis, in addition to its pulmonary effects, may in rare instances involve the myocardium, producing lesions varying from disseminated miliary tubercles to large, caseous, tuberculous masses. Obliterating endarteritis of the pulmonary vessels (sometimes unsatisfactorily called Ayerza's disease) is a very rare condition which usually does not have a luetic origin. The pathological picture is that of an occluding endarteritis of the smaller pulmonary vessels with dilatation of the pulmonary artery and hypertrophy of the right heart. Cheney²⁵ considers it to be a distinct disease entity, while Moschowitz²⁶

regards it, in the absence of proved etiology, as merely a syndrome which may be secondary to hypertension and sclerosis of the pulmonary circuit

There were 17 cases of chronic pulmonary disease in our series in which definite cardiac changes were observed. Pulmonary abscess, bronchopneumonia, bronchiectasis, and pulmonary tuberculosis were the most frequent disorders, though there were two cases of emphysema, one case of silicosis and emphysema, and two cases of endarteritis obliterans.

Generalized enlargement of the heart was noted in five cases, left ventricular hypertrophy in one, and right ventricular hypertrophy in four, although in this last group the total heart weight was within normal limits in two. Microscopic changes were not particularly important or characteristic.

In one case of miliary tuberculosis a few miliary tubercles were found in a heart which was otherwise normal, while in another case of tuberculosis the incidental finding of a small rhabdomyoma was the only cardiac abnormality. The other changes reported were enlarged fibers in a case of right-sided hypertrophy, associated with bronchiectasis and emphysema, fatty infiltration in a case of tuberculosis and chronic alcoholism, small areas of scarring in a case in which a positive Kahn reaction and aortic changes brought up the question of cardiovascular syphilis, and an eosinophilia in a case of obliterating endarteritis. Electrocardiograms showed left axis deviation in the case of left ventricular hypertrophy and in one case of generalized enlargement and right axis deviation in a case of right ventricular hypertrophy. In three cases, other than the one noted above, the Kahn reaction was positive, although there was no evidence of cardiovascular syphilis.

(C) *Acute Infections Other than Pulmonary* Acute infectious diseases in general cause no permanent injury to the heart muscle, though temporary functional derangement has been frequently observed. When there has been a concurrent intense toxemia, examination may show myocardial changes of a non-specific nature. Warthin¹² and others have described necrosis and hyaline degeneration of muscle fibers with the appearance of fatty changes and cloudy swelling in diphtheria, while Hamman³² found fragmentation and swelling of the muscle fibers, interstitial edema, and perivascular fibrosis in severe typhoid fever. In other acute infections similar pictures have been reported, when death has occurred while toxemia has been intense. However, the lack of permanent injury is indicated by the return of normal function after the infection has subsided. White and Jones³¹ were unable to find clinical evidence of cardiac damage in 100 cases five to eight years after severe diphtheria, while Brow,²⁸ in spite of Thayer's (quoted by Brow) assertion that elevated blood pressure and vascular sclerosis were frequent sequels of typhoid fever, found no indication of permanent ill effects in 65 cases of this disease one to 13 months after recovery. Rheumatic fever occupies a somewhat unique position among

acute infections, at least so far as cardiac involvement is concerned. Although endocardial damage is responsible for most of the late crippling effects, yet during the acute infection a pancarditis is almost the rule. After the acute disease is well established, the typical myocardial lesions are the Aschoff bodies, perivascular inflammatory reactions with round cell and giant cell infiltration. These lesions usually clear up after the acute infection has passed, although residual sclerosis has been reported.

That functional cardiac impairment does take place during the height of acute infectious disease is amply shown by electrocardiographic studies. Brow,²⁸ Burnett and Piltz,¹⁷ and others have reported electrocardiographic changes in diphtheria, rheumatic fever, typhoid fever, pneumonia, influenza, and other acute infectious diseases. Prolongation of the P-R interval, slurring of the QRS complexes, and inversion of the T-waves are the usual findings and indicate disturbance of the conduction mechanism and myocardium. In diphtheria, particularly, conduction changes varying from simple prolongation of the P-R interval to complete A-V block as well as alterations in the T-waves are frequently noted. Except in rare instances it is the rule for these signs to disappear in a few months. There were 35 cases in our series showing myocardial damage or hypertrophy in acute infectious diseases.

In the five cases of diphtheria, the gross changes were not remarkable except for slight to moderate enlargement in three. Microscopically four of them showed hyaline degeneration with necrosis of fibers and cellular infiltration. The two cases of typhoid fever had essentially normal hearts except for moderate increase in weight. Three cases of scarlet fever were included because of the focal necroses and cellular infiltration of the myocardium. In one of them the lesions suggested Aschoff bodies. In two of them, one associated with acute nephritis and the other with pyelonephritis, there was definite cardiac enlargement when the age of the patient was taken into consideration. Of eight cases of meningitis due to the meningococcus or the streptococcus, the heart weight was above the normal in seven. Microscopic examination showed focal necroses in three of these. A case of encephalitis and bronchopneumonia showed occasional necrotic fibers and slight increase in heart weight. In the remaining 16 cases pyogenic infections were the immediate causes of death. The diagnoses included septicemia, pyemia, purulent arthritis, osteomyelitis, localized abscesses, and peritonitis. Definite increase in weight was noted in 11 and slight increase in three. In six cases microscopic examination showed no abnormalities and in two it was not done. In the remaining eight cases changes varied from focal fibrosis to necrosis and actual abscess formation. Abscess formation in the heart was found in cases of pyemia and formed a part of the general process.

Electrocardiograms were taken in four of the diphtheria cases. In three of them there was definite evidence of disturbance in the conduction

mechanism, while the fourth was normal. A tracing was made in one of the pyemic cases and was not remarkable except for left axis deviation.

No case of acute rheumatic infection is included in this series because in each case there was some associated valvular disease. Rare cases do exist of myocardial rheumatic involvement with little or no valvular disease, but none were found in the groups from which our series was drawn.

(D) *Chronic Infections Other than Pulmonary* The effect of focal infections upon the heart is not very definitely understood. Bacterial endocarditis is infrequently associated with them, but no definite myocardial lesions have been found which may be related to focal infections. Aggravation of an existing heart disease or rarely minor arrhythmias may occur, but the relationship is far from certain.

There were seven cases of chronic non-pulmonary infectious disease with abnormalities of the heart without valvular deformities in our series. In five of them, the heart weight was definitely increased, in one the weight was borderline, and in one it was within normal limits. In three of the cases chronic infection of the kidneys undoubtedly produced some renal insufficiency, especially since in two cases only one kidney was functioning. In one case of luetic myelitis, the healed luetic aortitis and microscopic arterial changes may have accounted to some degree for the moderate increase in heart weight. Other microscopic changes were not remarkable except for the questionable Aschoff bodies in a case of a long-continued pyemic process with multiple septic joints.

3 DISEASES OF THE BLOOD

Enlargement of the heart in severe anemias has been noted clinically by several observers and has been confirmed at necropsy. Gautier³⁷ reported demonstrable enlargement in 20 of 22 patients with severe chlorosis, while other writers have published series of cases of pernicious anemia in which this phenomenon was noted in from 30 per cent to 95 per cent. Goldstein and Boas³⁴ found extension of the heart borders by percussion in 23 of 39 cases of pernicious anemia, six of them verified by roentgen-ray. Twelve of this group which came to autopsy showed marked cardiac dilatation with gross weights varying from 250 to 460 grams, averaging 330 grams. "Tigering" of the myocardium was observed in six cases. That these changes are not peculiar to pernicious anemia but accompany any severe anemia is demonstrated by the observations of Goldstein and Boas,³⁴ Ball,³⁸ and others. Ball cited a case in which electrocardiographic changes characteristic of left ventricular preponderance practically disappeared with restoration of the normal blood level.

Anoxemia has been suggested as the cause of the dilatation and is probably the principal factor at work. There is undoubtedly some degree of hypertrophy in long-standing anemias, which may result from the cardiac dilatation. Fahr and Ronzone³⁵ reported an increase of as much as 250

per cent in the minute volume of the heart output, in one case of severe pernicious anemia. This compensatory mechanism is made possible by accelerated beat, increased stroke volume, and decreased viscosity of the blood.

In leukemias there is, in addition to the marked accompanying anemia, the weight of the infiltrating cells, which may in some cases be sufficient to produce an appreciable increase in heart weight.

There were 27 cases of blood dyscrasias in our series: acute and chronic leukemia 17, aplastic anemia 3, hemolytic jaundice 2, pernicious anemia 1, purpura hemorrhagica 1, sickle cell anemia 1, agranulocytosis 1, and erythroblastosis neonatorum 1.

There were 17 cases of acute and chronic leukemia in this group. Among the adults with leukemia the heart weights varied between 200 and 498 grams with but six of the number above the normal limits. There did not seem to be any correlation between heart weight and the duration of the disease or the predominant type of cell. In the three children (cases 3, 6, and 13) the hearts were considerably heavier than one would expect at their ages. In almost all the 17 cases there was marked anemia, which in itself may cause dilatation and some hypertrophy of the heart. Grossly the hearts were described as pale, lax, flabby, and sometimes dilated, while microscopically there was considerable infiltration with leukemic cells in most cases, attaining in places the proportion of an actual tumor growth. Petechial hemorrhages were a fairly common finding. Among the other 10 cases of blood diseases five showed definite increase in heart weight. Dilatation, hypertrophy, petechial hemorrhages, and mottling of the myocardium were noted grossly, while microscopically, in those cases in which abnormalities occurred, diffuse fibrosis, petechial hemorrhages, and vacuolization of fibers were described. This last condition was found in three cases: one of aplastic anemia, one of sickle cell anemia, and one of erythroblastosis neonatorum. In the first two there was marked anemia, while in the last case death occurred so quickly that blood studies were not carried out. In a case of arsphenamine agranulocytosis, the cardiac enlargement was very striking, when the age is considered, although the anemia was not pronounced. Only one case of pernicious anemia was found in the series, probably because of the introduction of liver therapy during the past decade.

4 CORONARY OCCLUSION

The immediate effects of occlusion of a large branch of the coronary arteries may be extreme dilatation and failure of the heart. The part supplied by the occluded vessel becomes infarcted, and if the patient survives, the whole area eventually becomes fibrotic. The early dilatation to a large degree disappears, but if the infarcted area is large, hypertrophy of varying degrees takes place. Recently Smith and Bartels¹⁰ cited two cases of extensive coronary occlusion in which the heart weights were greatly

increased, there was enormous dilatation without much increase in thickness of the ventricular walls. These authors followed this report with a much larger series of 42 cases⁴¹ of coronary occlusion from which all other possibilities of hypertrophy had been eliminated. They calculated the normal heart weights by Smith's method and found a definite increase in weight of from 9 per cent to 108 per cent in 37 of the 42 cases, the actual weights varying between 265 and 715 grams. The average increase in weight above the calculated normal for the whole group was 44 per cent. From this study they concluded that coronary occlusion with cardiac infarction was a definite cause of hypertrophy.

There were five cases of coronary occlusion in our series in which there was neither history nor evidence of hypertension at the time of admission to the hospital. In addition there were four other cases of coronary occlusion with definite hypertension which were included under the heading "Hypertension with Other Complications."

Although all these hearts were very definitely above the normal weight (average 518 grams), it is difficult to draw conclusions from so small a group. A previous hypertension is almost impossible to exclude, since some of the patients were in a condition of shock on entering the hospital. The myocardial changes consisted of hypertrophy and of old or recent infarcts. The electrocardiographic changes, left axis deviation, bundle branch block, and altered QRS and T-waves are consistent with recent and old coronary occlusion and with hypertension.

5 CONGENITAL HYPERTROPHY OF THE HEART

According to Kugel and Stoloff⁴⁴ only 52 cases of congenital idiopathic hypertrophy of the heart had been reported up to 1933, in addition to the seven which they reported in April of that year. These authors consider that only those cases which show pure hypertrophy of the muscle fibers should be considered as idiopathic hypertrophy, and that if such changes as fibrosis or any kind of degeneration are present, the heart cannot then be said to be an example of idiopathic hypertrophy. Using this standard they found that only 17 out of 59 cases had "true idiopathic hypertrophy," the remaining cases showing changes secondary to some other process.

Many different causes for congenital hypertrophy of the heart have been suggested, but no one has been found to be operative in a considerable number of individuals. In one of our cases, which has already been reported,⁴⁵ glycogen storage (von Gierke's) disease was later found responsible, and there was a very unusual family history in that several members of the family had cardiac defects, thus suggesting the probability of an inheritance of a tendency to this cardiac anomaly. Bland, White, and Garland⁴⁸ have recently reported the case of a male infant dying at the age of three months, in whom at autopsy the left coronary artery arose from the pulmonary artery and the enlarged heart showed much disease of the left

ventricular myocardium, eight similar cases had been previously reported. Other possible etiological factors which have been mentioned as causes of cardiac hypertrophy in infancy besides congenital septal and valvular defects are infection, hypertension in the parents, enlarged thymus, and congenital medial sclerosis.

There were four cases of congenital hypertrophy in our series. In the first three this diagnosis was made clinically, while in the last the case was regarded as one of cardiac hypertrophy of unknown origin in an infant.

In our four cases the weight of the hearts was increased from two to six times the normal. Two of the hearts were described as dilated, one as enlarged, and one as enlarged with right ventricular hypertrophy and petechial hemorrhages over the left ventricular base. Microscopic changes were unimportant except for hypertrophied and vacuolated fibers in one of the cases. One case died of congestive failure, one of congestive failure and bronchopneumonia, one at birth, while the immediate cause of death in the fourth was uncertain.

6 HYPERTHYROIDISM

There has always been a division of opinion as to whether hyperthyroidism per se produces definite myocardial abnormalities, or whether the cardiac pathological changes are the result of increased metabolism. Recently Rake and McEachern⁵⁴ examined the hearts of 27 autopsied cases of hyperthyroidism, and, by comparing the results with those from supposedly normal hearts of similar age groups, found only five of the 27 with changes more marked than in the controls. Muscular scarring, perivascular fibrosis, cellular infiltration, and altered staining reactions were reported in the five cases noted above, with lesser degrees of the same findings in many others. The writers considered the picture to be merely an accentuation of normal katabolic changes brought on by the increased metabolic and cardiac activity and in no way peculiar to the hyperthyroid state. Kepler⁵⁰ studied 57 cases of exophthalmic goiter and 16 cases of toxic adenoma from the point of view of hypertrophy of the heart and found that 49 per cent of them showed an increase in weight when compared with the Smith standards. The body weights used in the calculations were those prior to the onset of the condition. Burnett and Durbin⁵² found evidence of definitely abnormal axis deviation in 24 of 62 patients—right in 7 and left in 17.

There were nine cases with the clinical diagnosis of hyperthyroidism which came to autopsy over this period. In seven of them the heart was described as normal. In the other two, one of them complicated by a moderate hypertension, the heart weight was moderately increased though the myocardium was apparently normal. The "bile staining," noted in one of them, was a part of a general icterus, while the rather high systolic pressure was probably secondary to the thyrotoxicosis rather than of the essential variety.

7 CARDIAC FAILURE OF UNCERTAIN ETIOLOGY

A few years ago Christian ³⁸ pointed out that there are a large number of cases of cardiac failure occurring in middle age for which there is no obvious reason. He stated that although arteriosclerosis, coronary disease, previous acute infections, or previous hypertension may account for some, yet in many no etiological agent is apparent. Clinically there is evidence of muscular deficiency, but physical examination and electrocardiographic studies may be entirely negative. Pathologically the hearts are often hypertrophied and may or may not show fibrosis.

There were eight cases in our series which seemed to fall into this group. In three of them there was a strong possibility of a previous hypertension, although the pressures recorded did not justify inclusion in that group.

Of these cases all except two were in the very upper limits of our age group. Cardiac enlargement, in two cases of marked degree, was noted in six instances. Failure to record the blood pressure in three cases naturally makes exclusion of hypertension impossible, while a marked anemia in another may well have been an etiological factor. Myocardial changes consisted of dilatation, hypertrophy, and gross and microscopic scarring. Electrocardiograms gave evidence of disturbed conduction, either in the bundle or in the ventricular muscle.

One of the cases (case 8 in the tables) is of particular interest because of the youth of the patient. On his first entry to the hospital he presented the picture of cardiac decompensation which was considered to be probably on a rheumatic basis, although no specific history was obtained. After a few weeks in the ward he was discharged greatly improved to a convalescent home where he remained off and on for eight months. At that time his symptoms returned and he reentered the hospital where he died in a short time. Autopsy did not explain the cause of his cardiac failure. Somewhat similar cases of idiopathic cardiac hypertrophy have recently been reported by Levy ⁴³

8 MISCELLANEOUS

Seventeen cases were of so varied a nature that they have been placed in a miscellaneous group. The diagnoses in this group include generalized malignancy 5, brain tumor 3, cirrhosis of the liver 2, rhabdomyoma 1, ruptured aortic aneurysm 1, gastric ulcer with hemorrhage 1, thrombosis of portal vein 1, nephrosis 1, enlargement of liver and spleen of unknown cause 1, and pregnancy and labor 1.

Of the five cases of generalized malignancy, four showed definite increase in heart weight with metastatic involvement of the myocardium in two. Cardiac enlargement was observed in all three cases of intracranial tumor and in one of them there was malignant involvement of the heart muscle. The largest heart in this group was associated with cirrhosis of the liver and luetic aortitis, it was impossible to tell if either factor was really connected with the hypertrophy. In the case of uncomplicated cir-

rhosis the enlargement was not so striking. In the remaining seven cases increase in heart weight was noted in six, and, with the exception of two cases, for no very obvious reason. In one case the myocardium was riddled with a rhabdomyoma, nodules of which partly occluded two valves, while in another, a 6 year old boy, degenerative changes in the myocardium were found with general glandular enlargement of unknown etiology. In the one case of nephrosis (case 15) the weight was well within normal limits, but atrophy and fatty infiltration of the myocardium were reported.

Although it is impossible to draw any conclusions from so varied a group, yet the frequent association of cardiac hypertrophy with malignancy is difficult to explain, except where metastatic involvement occurred. There was no marked degree of anemia in any of these cases, nor was there any other apparent cause of enlargement.

SUMMARY

An analysis has been made by us of 250 instances of myocardial abnormality in individuals under the age of 46 years without valvular disease or congenital defects found among 4,531 cases examined post mortem at the Massachusetts General and Boston City Hospitals.

There were 97 cases with hypertension in which the chief cardiac lesion was hypertrophy with diffuse or perivascular fibrosis in about 40 per cent.

There were 91 cases of acute and chronic infections in which cardiac abnormalities were observed. In acute pulmonary infections hypertrophy of the heart was frequently noted with dilatation, edema of the muscle, and occasionally focal necroses. In the chronic pulmonary infections generalized or right ventricular enlargement was noted in several cases without characteristic microscopic changes. In acute infections other than pulmonary, there occurred severe muscle damage in diphtheria, focal necroses frequently in severe toxemias, and occasional milary abscesses in extensive pyemias. In chronic infections other than pulmonary there was often moderate increase in heart weight with myocardial fibrosis in some cases.

There were 27 cases of various blood dyscrasias in which hypertrophy was noted in less than half, with microscopic changes consisting of fatty infiltration, slight fibrosis, petechial hemorrhages, and leukemic infiltration.

Nine cases of coronary thrombosis, five complicated by known hypertension, showed marked hypertrophy with recent or old infarction.

In four cases of congenital cardiac hypertrophy in infants, there was marked increase in heart weight with negligible microscopic changes except for hypertrophy and vacuolization of muscle fibers in one case.

In two cases of hyperthyroidism, one complicated by systolic hypertension, there was moderate cardiac enlargement without significant microscopic changes.

In eight cases of cardiac failure of uncertain etiology, hypertrophy and myocardial fibrosis were the most important lesions.

In seventeen miscellaneous cases no constant changes were observed, though the association of myocardial abnormalities with generalized and intracranial malignancy in several cases was interesting

We wish to express our thanks to Dr Paul D White for his never-failing aid in the assembling and critical analysis of our material. It was at his suggestion that this study was begun and it was through him that it finally reached its present form. We wish also to acknowledge the courtesy and cooperation of the Pathological Departments of the Massachusetts General and Boston City Hospitals in granting permission to use their material

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THE SIGNIFICANCE OF SPECIFIC PNEUMOCOCCUS TYPES IN DISEASE, INCLUDING TYPES IV TO XXXII (COOPER) *

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THE recent increase in the use of specific serum for the treatment of pneumonia has been accompanied by a growing interest in the newer types of pneumococci ¹ in many parts of this and other countries. It seems appropriate, therefore, to present a brief résumé of 3682 cases admitted to the Boston City Hospital, from which pneumococci were cultured and typed with the aid of serums for these new types. Approximately one-third of these cases, previously reported,² occurred before June 1, 1932 and were typed with serums for Types I to XX. The remaining cases were admitted before July 1, 1936 and were typed with serums for Types I to XXXII, inclusive.

PATIENTS, SOURCES OF PNEUMOCOCCI, AND METHODS

These are described in previous papers ³ in which selected groups of cases were analyzed in considerable detail. The serums used in the classification of pneumococci Types IV to XXXII were obtained through the generosity of Dr. William H. Park and the late Miss Georgia Cooper of the Bureau of Laboratories of the New York City Department of Health. The bacteriologic and pathologic data were made available through the kindness of Dr. Frederick Parker, Jr. and Dr. Robert N. Nye of the Mallory Institute of Pathology of the Boston City Hospital. To them, to the resident and visiting staffs of the Boston City Hospital, and to the physicians and laboratory assistants who, at different times, participated directly in this study, the author acknowledges his gratitude.

ANNUAL AND MONTHLY INCIDENCE OF THE VARIOUS PNEUMOCOCCUS TYPES

The total number of cases of pneumococcic infections varied considerably from year to year (table 1) †. The annual incidence of some of the individual pneumococcus types fluctuated even more widely. Noteworthy is the sharp increase in the number of cases of infection with Types II, V and VII pneumococci during the 1935 to 1936 season. The mortality also varied in different seasons ^{3c, d}.

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† In the tables, the Types XXVI and XXX have been omitted. The former is probably identical with Type VI and the latter is either closely related to or identical with Type XV. Type XXX was identified in two cases, one with lobar pneumonia, the other with a common cold, these are included with the Type XV cases.

TABLE I
Annual Incidence of Infections with the Various Types of Pneumococci
(Boston City Hospital, November 1929 to June 1936)

Type	1929- 1930	1930- 1931	1931- 1932	1932- 1933	1933- 1934	1934- 1935	1935- 1936	Totals
I	117	109	81	112	153	141	160	873
II	51	60	55	54	25	18	90	353
III	57	69	65	91	101	88	101	572
IV	4	5	11	15	12	23	15	85
V	13	20	17	55	32	26	105	268
VI	3	2	18	21	20	19	14	97
VII	14	24	20	20	28	22	67	195
VIII	19	16	40	50	33	72	49	279
IX	2	9	6	11	8	6	14	56
X	1	22	13	16	11	23	16	102
XI	0	13	9	5	6	13	21	67
XII	2	6	3	9	7	18	12	57
XIII	1	1	5	8	5	4	9	33
XIV	0	9	11	15	26	14	30	105
XV	2	2	2	3	3	4	2	18
XVI	0	0	2	2	2	6	2	14
XVII	0	0	9	6	6	11	17	49
XVIII	16	7	12	10	12	18	20	95
XIX	—	1	7	10	10	12	7	47
XX	—	—	17	16	22	15	23	93
XXI	—	—	0	1	4	9	12	26
XXII	—	—	1	6	2	11	6	26
XXIII	—	—	—	0	1	2	7	10
XXIV	—	—	—	3	0	4	1	8
XXV	—	—	—	2	0	0	5	7
XXVII	—	—	—	0	0	1	1	2
XXVIII	—	—	—	0	0	3	3	6
XXIX	—	—	—	1	1	4	7	13
XXXI	—	—	—	1	0	4	0	5
XXXII	—	—	—	0	0	1	4	5
Neg I-XX	44	36	28	3	—	—	—	111
Neg I-XXXII	—	—	3	0	0	0	2	5
TOTAL	346	411	435	546	530	592	822	3682

The month of greatest incidence of all pneumococcic infections was always one of the winter months (January to March), but it varied in different years. While the peak of incidence was usually the same for most of the common types, disproportionate increases occurred at various times for individual types.^{3b}

OCCURRENCE OF SPECIFIC PNEUMOCOCCUS TYPES IN DIFFERENT DISEASES

All of the cases with typed pneumococci were divided into six groups and the number and percentage of cases of each type occurring within each category are given in table 2. All patients over 12 years of age are listed as adults. The groups may be described briefly.

A Under *lobar pneumonia* are included all cases with uniform consolidation in one or more lobes of the lung according to the best evidence obtainable from pathological, roentgenological, or physical examination. In

table 2, the cases in which there was additional patchy or atypical solidification in other parts of the lung were included in this category. The most frequent types in this group were Types I, III, II, V, VIII, and VII, in the order named. These six types together accounted for 79 per cent of the cases of lobar pneumonia.

TABLE II
Occurrence of Pneumococcus Types in Disease

Type	A Lobar Pneu- monia in Adults *		B Atypical Pneu- monia in Adults		C Em- pyema on Ad- mission in Adults		D Pneu- monia and/or Em- pyema in Children		E Focal Infec- tions (No Pneu- monia)		F Carriers and Re- spiratory Infec- tions without Pneu- monia		All Cases	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
I	654	29.3	28	4.5	27	3.9	118	55.1	34	14.0	12	3.9	873	23.7
II	294	13.2	15	2.4	10	1.5	9	4.2	17	7.0	8	2.6	353	9.6
III	335	15.0	99	16.0	5	.7	6	2.8	76	31.3	51	16.6	572	15.5
IV	46	2.1	18	2.9	1	.1	4	1.9	6	2.5	10	3.2	85	2.3
V	191	8.6	30	4.8	5	.7	19	8.9	17	7.0	6	1.9	268	7.3
VI	28	1.3	30	4.8	3	.4	8	3.7	10	4.1	18	5.8	97	2.6
VII	128	5.7	32	5.2	4	.6	2	0.9	10	4.1	19	6.2	195	5.3
VIII	159	7.2	68	11.0	8	1.2	4	1.9	22	9.1	18	5.8	279	7.6
IX	30	1.3	12	1.9	2	.3	3	1.4	2	0.8	7	2.3	56	1.5
X	37	1.7	40	6.5	1	.1	2	0.9	5	2.1	17	5.5	102	2.8
XI	29	1.3	18	2.9	0	0	4	1.9	8	3.3	8	2.6	67	1.8
XII	38	1.7	8	1.3	1	.1	4	1.9	3	1.2	3	1.0	57	1.5
XIII	13	0.6	12	1.9	0	0	0	0	2	0.8	6	1.9	33	0.9
XIV	51	2.3	24	3.9	1	.1	15	7.0	7	2.9	7	2.3	105	2.9
XV	7	0.3	6	1.0	0	0	0	0	0	0	5	1.6	18	0.5
XVI	4	0.2	8	1.3	0	0	1	0.5	0	0	1	0.3	14	0.4
XVII	19	0.9	20	3.2	0	0	2	0.9	1	0.4	7	2.3	49	1.3
XVIII	38	1.7	32	5.2	0	0	1	0.5	4	1.6	20	6.5	95	2.6
XIX	19	0.9	12	1.9	0	0	4	1.9	5	2.1	7	2.3	47	1.3
XX	36	1.6	35	5.7	0	0	4	1.9	3	1.2	15	4.9	93	2.5
XXI	9	0.4	9	1.5	0	0	1	0.5	3	1.2	4	1.3	26	0.7
XXII	10	0.4	10	1.6	0	0	0	0	2	0.8	4	1.3	26	0.7
XXIII	2	0.1	3	0.5	0	0	1	0.5	0	0	4	1.3	10	0.3
XXIV	0	0	3	0.5	0	0	0	0	0	0	5	1.6	8	0.2
XXV	3	0.1	2	0.3	0	0	0	0	1	0.4	1	0.3	7	0.2
XXVII	1	0	0	0	0	0	0	0	0	0	1	0.3	2	0.1
XXVIII	0	0	4	0.6	0	0	0	0	1	0.4	1	0.3	6	0.2
XXIX	4	0.2	4	0.6	0	0	0	0	2	0.8	3	1.0	13	0.4
XXXI	3	0.1	0	0	0	0	0	0	0	0	2	0.6	5	0.1
XXXII	3	0.1	1	0.2	0	0	0	0	0	0	1	0.3	5	0.1
Neg I-XX †	35	1.6	35	5.7	1	.1	1	0.5	2	0.8	37	12.0	111	3.0
Neg I-XXXII	3	0.1	1	0.2	0	0	1	0.5	0	0	0	0	5	0.1
TOTALS	2229	100	619	100	69	100	214	100	243	100	308	100	3682	100

* Includes cases with lobar pneumonia in one or more lobes and atypical in other parts.

† Some of the cases previously included (2) have been omitted because of insufficient data to classify the organisms as pneumococci.

B All cases with patchy or with peribronchial pulmonary consolidation were included as *atypical pneumonia*,⁴ a designation used throughout this paper instead of the term "bronchopneumonia" The most frequent types in these cases were Types III, VIII, X, XX, XVIII, and VIII which, together, accounted for one-half the cases of this group

The pneumococcus types in the cases of pneumonia in adults (groups *A* and *B*) were obtained from cultures of either sputum, blood, lung, infected exudates or autopsy material, or from more than one of these sources In about half the cases the sputum was the only source

C Cases of *adults with empyema* present at the time of admission, in which the pneumococcus type was obtained from the infected pleural exudate, are listed separately The types most frequent in this group were the same, except for order, as among the cases of lobar pneumonia in adults, namely Types I, II, VIII, III, V, and VII, which accounted for 84 per cent of the group

D Most of the cases of *pneumonia in children*, with or without empyema, were typed either from pleural exudate or from material obtained at autopsy In occasional cases, the pneumococci were obtained from blood cultures or, more rarely, from sputum or throat cultures About two-thirds of these cases had empyema Type I alone accounted for more than half of the cases Types V, XIV, II, VI and III, respectively, ranked next in frequency These six types included 82 per cent of the cases of this group

E Under *focal infections* are included cases in all age groups in which the pneumococci were cultured from the infected focus and in which there was no evidence of pneumonia at the time Type III organisms were most frequent in this group, with Types I, VIII, II, and V following in the order named Together, these five types included slightly more than one-half the cases in this category

F The last group includes cases of *acute or chronic respiratory infections* where there was no evidence of pneumonia attributable to the pneumococcus This group also includes cases that may be termed *carriers*, in whom the pneumococci were obtained from routine nasal, pharyngeal, or sputum cultures taken during the course of other diseases and in whom there was no evidence of infection attributable to the pneumococcus In this group, Types III, XVIII, VII, VI, VIII, X, and XX were most common, in that order, these seven types constituting more than half of the total

CASES WITH AUTOPSY

In 764 of the fatal cases there was an opportunity to ascertain at necropsy the relationship of the pneumococcus to the infection The classification of the autopsied cases according to the pneumococcus type, with particular reference to the character of the pulmonary lesion in the cases with pneumonia, is given in table 3 The six most frequent types in the cases with lobar pneumonia were the same, in essentially the same order, as noted in

table 2, namely, Types I, III, II, V, VII, and VIII, these types accounting for 83 per cent of the cases. One-sixth of all the cases that had lobar pneumonia at autopsy also showed some areas of atypical consolidation in other portions of the lung.

TABLE III
Occurrence of Pneumococcus Types in Autopsied Cases

Type	Lobar Pneumonia		Atypical Pneumonia		Mixed Lobar and Atypical Pneumonia	Focal Infection without Pneumonia	No Proved Relation to Disease	Total	
	Number	Per cent	Number	Per cent	Number	Number	Number	Number	Per cent
I	104	30.7	21	7.2	13	5	2	145	19.0
II	43	12.7	11	3.8	2	8	1	65	8.5
III	81	23.9	47	16.2	11	17	4	160	20.9
IV	14	4.1	9	3.1	2	2	2	29	3.9
V	32	9.4	22	7.6	7	5	0	66	8.6
VI	5	1.5	15	5.2	0	1	1	22	2.9
VII	17	5.0	16	5.5	5	3	0	41	5.4
VIII	17	5.0	28	9.7	3	5	2	55	7.2
IX	4	1.2	6	2.1	0	1	1	12	1.6
X	4	1.2	19	6.6	2	1	0	26	3.4
XI	1	0.3	8	2.8	0	4	0	13	1.7
XII	3	0.9	9	3.1	1	1	0	114	1.8
XIII	1	0.3	4	1.4	0	0	0	5	0.7
XIV	6	1.8	8	2.8	5	0	0	19	2.5
XV	0	0	0	0	0	0	1	1	0.1
XVI	0	0	6	2.1	0	0	0	6	0.8
XVII	0	0	7	2.4	1	0	0	8	1.0
XVIII	4	1.2	12	4.1	1	1	1	19	2.5
XIX	1	0.3	3	1.0	1	1	0	6	0.8
XX	0	0	14	4.8	1	1	0	16	2.1
XXI	1	0.3	2	0.7	0	1	0	4	0.5
XXII	1	0.3	5	1.7	0	1	1	8	1.0
XXIII	0	0	3	1.0	0	0	0	3	0.4
XXIV	0	0	1	0.3	0	0	0	1	0.1
XXV	0	0	0	0	0	1	0	1	0.1
XXVII	0	0	1	0.3	0	0	0	1	0.1
XXVIII	0	0	1	0.3	0	1	0	2	0.3
XXIX	0	0	2	0.7	0	1	1	4	0.5
Neg I-XX	0	0	10	3.4	0	1	1	12	1.6
TOTALS	339	100	290	100	55	62	18	764	100

Among the cases in which only atypical pneumonia was found in the lungs at autopsy, Types I and V ranked high in incidence, in addition to the types noted previously for the entire group. The most common types among these cases, in the order of their frequency were Types III, VIII, V, I, X, VI, VII, XX, and XVIII, these nine types including 68 per cent of the total. The discrepancy between the relative frequency in the entire group and in the autopsied cases is explicable on the basis of differences in mortality rates, as will be noted below.

TABLE IV

Focal Purulent Infections with the Various Types of Pneumococci

Pneumo- coccus Type	Cases without Pneumonia				Cases Complicating Pneumonia † (adults)							
	Otitis Media and/or Mastoiditis	Meningitis	Peritonitis	Others *	Empyema	Pericarditis	Lung Abscess	Endocarditis	Meningitis	Otitis Media	Peritonitis	Subcutaneous Abscesses
I	10	4	5	14	93	13	16	5	2	11	2	12
II	4	4	2	7	18	4	10	6	6	5	0	6
III	37	15	9	15	37	19	28	2	3	6	3	4
IV	1	4	0	1	4	0	1	0	1	1	0	0
V	9	3	3	2	31	6	8	3	3	6	6	4
VI	2	2	3	3	3	5	4	1	0	0	0	0
VII	4	4	1	1	9	5	1	3	3	2	0	1
VIII	1	4	7	11	15	1	5	2	8	1	1	2
IX	0	2	0	0	4	0	2	0	0	0	0	0
X	0	4	0	1	3	1	1	1	1	0	0	0
XI	1	3	0	4	1	0	1	0	0	0	0	0
XII	0	2	0	1	3	0	1	0	0	0	0	0
XIII	0	2	0	0	1	1	1	0	0	0	0	0
XIV	2	2	0	3	5	2	4	1	2	0	1	0
XV	0	0	0	0	0	0	0	0	0	0	0	0
XVI	0	0	0	0	0	1	0	0	0	0	0	0
XVII	0	1	0	0	4	0	1	0	0	0	0	0
XVIII	1	2	1	0	4	0	3	3	1	0	0	2
XIX	2	2	0	1	3	0	0	1	0	2	0	2
XX	0	2	1	0	1	0	2	0	1	1	2	1
XXI	0	0	3	0	0	0	2	0	0	0	0	0
XXII	0	1	0	1	3	0	1	0	0	0	0	0
XXIII	0	0	0	0	0	0	2	1	0	0	0	1
XXIV	0	0	0	0	0	0	0	0	0	0	0	0
XXV	0	1	0	0	0	0	1	0	0	0	1	0
XXVII	0	0	0	0	0	0	0	1	1	0	0	0
XXVIII	0	1	0	0	0	0	0	0	0	0	0	0
XXIX	1	0	1	0	1	0	1	0	0	0	0	1
XXXI	0	0	0	0	0	0	0	0	1	0	0	0
XXXII	0	0	0	0	0	0	0	0	0	0	0	0
Neg I-XX	0	1	0	1	4	1	0	1	0	0	0	0
Neg I-XXXII	0	0	1	0	0	0	0	0	0	0	0	0
TOTALS	75	66	37	65	247	59	96	30	33	35	16	36

* These include the following

Endocarditis 3 cases (Types I, VIII and X, 1 each),

Purulent arthritis 3 (Types I, XII, XIV, 1 each),

Osteomyelitis 7 (Type II, 2 cases, Types I, VIII, XI, XIX, XXII, 1 each),

Acute sinusitis 6 (Types II and VIII, 2 each, Types I, VI, 1 each),

Pulmonary abscesses 4 (Types III and V, 2 each),

Subcutaneous abscesses 10 (Type III, 3, Types II and XI, 2 each, and Types VII, VIII and XIV, 1 each),

Puerperal sepsis 3 (Type I, 2 and Type VIII, 1),

Bacteremia (positive blood culture, source not discovered) 18 (Types I and VIII, 4 each, Types II and III, 3 each, Types IV, VI, XI and Neg I to XX, 1 each)

Also one case each of Pericarditis, Type I, Infected hemothorax, Type I, Acute cystitis, Type III, Acute cholecystitis, Type III, Peritonsillar abscess, Type III, Mediastinitis, Type III, Subphrenic abscess, Type III, and Ulcerative colitis, Type IV

† The following are not listed

Arthritis 8 cases (Type I, 5, Type II, 1 and Type III, 2),

Parotitis 6 (Type I, 4, Types II and III, 1 each),

Conjunctivitis 4 (Type II, 1, Type III, 2, Type VIII, 1),

Liver abscess 1 (Type XI)

Empyemas in children and those present on admission in adults are listed in table 2 (D and B)

FOCAL PURULENT PNEUMOCOCCIC INFECTIONS

The numbers of cases in which each of the various types of pneumococci were cultured from focal infections, including those complicating pneumonia, are shown in table 4. Middle ear and mastoid infections were the most common in the cases without pneumonia, the Type III pneumococcus being the causative organism in about half of these cases. Meningitis, with or without middle ear or mastoid infection, was next in frequency and peritonitis ranked third. Of interest are the 18 cases of bacteremia, mentioned in the footnote to the table, in which neither pneumonia nor purulent foci were found even at the autopsy, which was performed in almost all of these cases.

Among the cases of pneumonia in adults, empyema was the most frequent purulent complication. Type I was most frequent in these cases as it was in the empyemas of children and in the adults who had empyema at the time of admission to the hospital (table 2). Lung abscesses or focal areas of necrosis were next in frequency, the most common organism being the Type III. Almost all of these were first observed at autopsy and a large proportion were seen only in the microscopic sections. The pneumococci in the latter cases were obtained from the infected lung. Pericarditis ranked third in frequency and, like endocarditis, was usually diagnosed at autopsy.

PNEUMONIA IN ADULTS

The percentage of incidence and of mortality among the pneumonias caused by the more frequent of the pneumococcus types is analyzed in table 5 with respect to three important features, each of which may be considered separately.

Lobar Pneumonia and Atypical Pneumonia There were cases of lobar pneumonia and of atypical pneumonia due to almost every one of the pneumococcus types (table 2). About one-fifth of all the cases of pneumococcus pneumonia had only atypical pulmonary consolidation. Types I and II stand out from among all the others as causing typical lobar pneumonia with the greatest regularity. Only 4 and 5 per cent of the cases of pneumonia due to these types, respectively, had only atypical involvement, and an additional smaller number of cases with lobar pneumonia due to these types had atypical consolidation in other portions of the lung. Among the other frequent types, more than two-thirds of the cases due to Types III, IV, V, VII, IX, XII, and XIV were lobar pneumonia, whereas about one-half of those caused by Types VI, X, XVII, XVIII, XX, and those with higher type designations were atypical.

The mortality was considerably higher among the cases with atypical pneumonia. This was true for all the cases, as well as for the cases within each type, the only exceptions being those with the Type III pneumococcus. Bacteremia was only half as frequent among the cases with atypical pneumonia as among those with lobar pneumonia. On the other hand, almost

Pneumococcus Pneumonia in Adults (Over 12 years of age)

Analysis of the relative incidence and mortality, for each type, of

(1) Lobar pneumonia and atypical pneumonia, (2) So-called secondary pneumonia, and (3) Bacteremia

[illegible]

* Specific types are listed separately when there were more than 30 cases of pneumonia

† Including cases in which the pneumococcus failed to agglutinate in sera of Types I to XX or I to XXXII

† Calculated on the basis of patients having blood cultures made

two-thirds of the former cases were secondary to other serious illnesses, as compared with only 10 per cent of the latter. The higher mortality among the cases with atypical pneumonia, therefore, is probably attributable to factors within the host rather than to difference in virulence of the organism. The much greater frequency of atypical pneumonias in persons over 70 years of age (17 per cent of all the atypical cases as compared with 5 per cent of the lobar pneumonias) lends further support to this view.

"Secondary" Pneumonia As in previous studies,³ cases occurring as terminal events or as acute episodes in the course of other serious illness and those complicating parturition, the puerperium, surgical operations, or other serious acute infectious diseases were called "secondary." All other cases, including those with antecedent simple infections of the upper respiratory tract, "grippe," influenza, or bronchitis were called primary. Among the cases with atypical pulmonary involvement, the secondary pneumonias were more than six times as frequent as among the cases with lobar consolidation. The mortality was about twice as great among the secondary as among the primary pneumonias. The greater incidence of secondary pneumonias thus serves to explain the greater mortality among the cases of atypical pneumonia.

Bacteremia The percentage of cases of pneumonia in which pneumococci were cultured from the blood varied with the different types. Bacteremia was much less frequent among the cases with atypical pneumonia than among those with lobar pneumonia. In general the mortality among the cases of lobar pneumonia corresponded to the incidence of bacteremia,⁵ but this was not true for all the types of pneumococci. The mortality among the bacteremic cases was uniformly higher, and averaged about twice as high as among those with sterile blood cultures. This was true irrespective of the character of the pulmonary lesion.

Serum treatment was carried out almost exclusively in cases of lobar pneumonia due to Types I, II, V, and VII. Only the gross mortalities are given here and indicate a reduction to about one-half the mortality in non-serum treated cases. The results of serum therapy in these cases are presented in greater detail in other publications.^{3a, 6}

Age Incidence The highest incidence of lobar pneumonia occurred in the fourth and fifth decades of life, declining rapidly thereafter, in the atypical pneumonias the peak was in the sixth decade and there was almost no decline in the next two decades. Among the cases of lobar pneumonia of the more common types, those due to Types II, V, and VII each showed their highest incidence in the fourth decade. Those due to Type III had a peak of incidence among the cases in the sixth decade of life, while the cases of Types I and VIII pneumococcus lobar pneumonia were most prevalent in the fifth decade.

MIXED INFECTIONS

There were 424 cases of pneumonia in which, in addition to the pneumococcus of the type under which the case was classified, other pathogenic organisms were obtained. These were cultured from sputum or from other

TABLE VI
Mixed Infections

	Total Number of Cases	Other Organisms in Cases of Pneumonia								Cases Listed with Other Types	
		Other pneumococcus types	<i>Streptococcus hemolyticus</i>	<i>Streptococcus viridans</i>	<i>Staphylococcus aureus</i>	<i>Bacillus mucosus capsulatus</i>	<i>Haemophilus influenzae</i>	Tubercle bacilli	Miscellaneous	Pneumonia Cases	Cases without Pneumonia
I	74	23*	25	8	14	5	7	5	6	8	3
II	28	6	12	3	7	1	5	3	0	4	0
III	61	21*	21	6	14	6	14	0	3	19	1
IV	14	2	3	2	2	3	5	1	5	5	0
V	35	12	17	1	7	1	6	0	1	3	1
VI	14	2*	2	2	4	3	3	1	1	3	0
VII	22	6	9	3	8	0	7	3	1	0	1
VIII	29	11	11	1	3	1	3	3	2	8	3
IX	9	1	3	2	2	1	2	2	0	2	0
X	21	3*	8	0	8	1	5	3	2	8	1
XI	10	5	4	0	2	0	4	0	0	5	1
XII	6	0	0	0	2	1	4	0	0	1	1
XIII	4	0	1	0	1	1	0	2	0	1	0
XIV	13	2	3	2	1	1	4	2	0	3	0
XV	2	0	0	0	0	0	1	0	2	2	0
XVI	5	1	1	1	0	0	1	1	1	2	0
XVII	12	1	3	0	3	1	5	0	0	2	1
XVIII	11	2	3	2	4	0	4	1	1	5	0
XIX	7	0	4	0	2	1	1	0	1	4	2
XX	15	2	6	1	2	1	4	1	4	8	4
XXI	6	0	2	0	2	1	3	0	0	4	3
XXII	11	2	3	0	2	0	7	1	1	0	0
XXIII	4	0	1	0	1	0	2	0	1	1	0
XXIV	1	0	1	0	1	0	0	0	0	3	0
XXV	2	1*	0	0	1	0	0	0	1	0	0
XXVIII	2	0	0	0	0	1	0	0	1	0	0
XXIX	4	0	2	0	1	1	1	0	0	2	1
XXXI	0	0	0	0	0	0	0	0	0	2	1
XXXII	2	0	1	0	0	1	0	0	0	0	0
Neg I-XX	—	—	—	—	—	—	—	—	—	1	0
Neg I-XXXII	—	—	—	—	—	—	—	—	—	2	0
TOTAL	424	103	145	34	94	32	98	29	34	108	24

* 1 case had pneumococci of 2 other types

sources during the acute illness, early in convalescence or at autopsy. Pyogenic organisms other than pneumococci, when obtained from sputum, were listed only when they were predominant in a good specimen or when they were cultured from the heart's blood of an injected mouse. Only hemolytic

strains of *Staphylococcus aureus* were included. Tubercle bacilli were noted whenever they were recognized in stained smears of sputum or pulmonary exudate. The number of cases in which various organisms were obtained in the pneumonias due to the various pneumococcus types is shown in table 6.

In 103 cases multiple pneumococcus types were isolated, five of these cases yielding three distinct types. The most frequent other organisms were *Beta hemolytic streptococcus*, *Hemophilus influenzae*, *Staphylococcus aureus hemolyticus*, *Streptococcus viridans*, and *Bacillus mucosus capsulatus* (Friedlander), in that order. Occasional instances of focal infections with colon bacillus, *Bacillus welchii*, or other organisms were noted as complicating the pneumococcus pneumonia. In other cases, the pneumococcus pneumonias occurred as a complication of other infections during which the causative agent, notably typhoid and paratyphoid bacilli were cultured.

The number of cases of pneumonia in which each of the various pneumococcus types occurred as a mixed infection, is also shown in table 6. The last column gives the distribution of types among 24 instances in which two types of pneumococci were identified among cases without pneumonia.

The significance of the various organisms in cases of pneumonia with mixed infection varies with each case. This has been discussed elsewhere.⁷

COMMENT

Type-specific antipneumococcic serum, within its limitations, is the only curative agent thus far recommended for the treatment of pneumonia which has stood the tests of experience, experiment, and critical analysis. The extension of serological typing to include practically all strains of pneumococci,¹ and the studies of the prevalence of these new types in health⁸ and disease,^{1, 2, 9} in addition to its great importance for the better understanding of the clinical, immunologic, and epidemiologic features of pneumococcic infections, has already proved useful in extending the field of specific serum therapy and holds promise for further practical benefits. Bullowa¹⁰ has reported favorable results in the treatment of cases of pneumonia due to Types VII, VIII, XIV, and V pneumococci, and equally promising results were observed in the treatment of small groups of cases of Type V and Type VII pneumococcus pneumonia in this clinic.^{6a, e}

It was not possible, in the space available, to analyze the material in any greater detail or to discuss the many possible implications of the findings recorded. Some of the clinical features of the more common types³ and the details of specific therapy⁶ in the present cases have been considered elsewhere. Other features of selected groups of cases, as well as the comparative significance of organisms other than the pneumococci⁷ are left for separate consideration. It is hoped that the material here presented will help somewhat in the orientation of those interested in this rather extensive field of pneumonia and pneumococcic infections.

SUMMARY

A series of 3682 cases is presented from which specific types of pneumococci were obtained and classified with the aid of the newer serums of Cooper¹. These cases occurred at the Boston City Hospital between November 1929 and June 30, 1936.

The incidence of the various types in different seasons and in different diseases and particularly in lobar pneumonia and atypical pneumonia (bronchopneumonia) is indicated.

The mortality rates in the cases of pneumonia in adults is noted with respect to (1) The type of infecting pneumococcus, (2) the character of the pulmonary lesion, (3) the presence of bacteremia, (4) the presence of other serious illness (secondary pneumonias), (5) serum therapy.

The incidence of mixed infections with pneumococci and other significant organisms is shown.

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AN OUTBREAK OF TRICHINIASIS IN CENTRAL OHIO AND THE USE OF THE BACHMAN INTRADERMAL SKIN TEST

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THE infrequency with which trichiniasis is recognized in man restricts the opportunity to study this disease and makes it important to utilize all cases whenever possible for the investigation of the Bachman intradermal test

The consumption of raw or inadequately cooked meat is more common in this country than is generally appreciated. While this is often done inadvertently, there are many who, from choice, eat raw sausages or other forms of pork deliberately, and these individuals constitute the majority of the more severe cases of trichiniasis.

The discovery and development of our knowledge of human trichiniasis has been reviewed recently, notably by McDonald,¹ and this will not be discussed here.

In the state of Ohio trichiniasis is not rare, although it is not often recognized. Doran² states that only two cases have appeared at St. John's Hospital, Cleveland, Ohio, in the past 16 years. At Grant Hospital, Columbus, Ohio, we could find records of only one case since 1925. The disease has been reportable to the Ohio State Department of Health since August 1928. From this date until March 1936, 96 cases have been reported, and of this number eight have died, a mortality of 8.33 per cent. The distribution of these cases is recorded in table 3.

Relatively few reports concerning the use of the Bachman test are to be found in the literature, in spite of the fact that Bachman³ first described the method in 1928. As late as 1931 an epidemic was reported in Pennsylvania by Aldridge⁴ with no mention of the test.

Bachman describes the preparation of his antigen thus: "The larvae are separated by artificial digestion and thoroughly washed free from host proteins—dried at 47° C. in a vacuum oven over sulphuric acid and thoroughly pulverized. Test antigen is prepared from a 1 per cent suspension of the dried pulverized trichinella powder extracted at room temperature for a day or longer in Coca's solution—then centrifuged at high speed for 15 minutes and the supernatant fluid used as the test antigen."

The powdered trichinella material is not available commercially at the present time.†

The antigen we used was prepared at Grant Hospital by O. H. Lausa. His technic was as follows: "Take 5 mg. of the dried trichinella powder

* Received for publication June 20, 1936.

† We wish to thank Dr. Benjamin Schwartz of the United States Department of Agriculture for supplying the necessary material.

Add 5 c c of Coca's solution and allow to stand at room temperature for 24 hours Then filter through a Berkefeld filter Culture to test for sterility Place in vaccine ampoules for use" The pH was about 8

CASE REPORTS *

These cases will be divided into two sections The first section will comprise the epidemic group, the second will be individual cases occurring at the same time in Columbus with different sources of infection

TABLE I
Data on Cases of Diagnosed Trichiniasis

Case	Ingestion of pork	Onset of symptoms	Eosinophilia		Bachman Intradermal Test		
			Admission	10 days later	1-1000	1-10,100	Control
Section I							
1 C M	Dec 24-Jan 10	Jan 8, 1936	5%	31%	+++	+	0
2 E B	Jan 1, 1936	Jan 4, 1936	70%	43%	+++	+	0
3 L E	Dec 24, 1935	Dec 28, 1935	33%	57%	++	+	0
4 R B	Dec 24, 1935	Dec 28, 1935	51%	20%	++	+	0
5 M T	Jan 1, 1936	Jan 4, 1936	47%	67%	++	+	0
6 E T	Jan 1, 1936	Jan 4, 1936	21%	32%	++	+	0
Section II							
1 C H	June '35-Jan '36	Jan 14, 1936	72%	?	+++	++	0
2 G R	Jan 5, 1936	Jan 14, 1936	31%	85%	+++	++	0

TABLE II
Control Tests

Case No	Race	Diagnosis	Age	Eosinophile count	Bachman Skin Test		
					1-1000	1-10,000	Control
1 W K	W	Gastric carcinoma	83	0	0	0	0
2 L R	Eth	Chronic heart disease	45	2%	0	0	0
3 H T	Eth	Luetic aortitis	56	2%	0	0	0
4 C F	Eth	Gangrene of toe	69	0	0	0	0
5 M B	W	Rheumatoid arthritis	47	0	0	0	0
6 L L	W	Chronic cardiac disease	40	4%	++	+	0
7 L A	W	Broncho-pneumonia	72	0	0	0	0
8 E I	W	Cardio-vascular renal dis	49	1%	0	0	0
9 I G	W	Malignancy of cervix	63	0	0	0	0
10 W R	W	Arteriosclerosis	64	4%	0	0	0
11 W B	W	Tabes dorsalis	30	0	0	0	0
12 J C	W	Ascites	74	2%	0	0	0
13 J H	W	Hypertrophic arthritis	79	0	0	0	0

*I wish to thank Dr C Joseph DeLor of University Hospital and Dr Thomas E Rardin and Miss Marcella Huercamp of St Francis Hospital for their help in the making of these tests and the presentation of the case reports

TABLE III
Cases of Trichiniasis Reported in Ohio

County	1929	1930	1931	1932	1933	1934	1935	1936	Total
Allen	4								4
Auglaize				1	8		7		16
Belmont	4								4
Cuyahoga	5	1	3	15	1	6	9		40
Darke							5		5
Erie					1				1
Jefferson						1		4	5
Mercer							3		3
Montgomery						1			1
Preble							1		1
Putnam								3	3
Shelby							10		10
Miami					1		2		3
Total	13	1	3	16	11	8	37	7	96

Deaths from Trichiniasis in Ohio

County	1931	1932	1933	1935
Darke				2
Franklin		1	1	
Hamilton			1	
Summit	1			
Trumbull		1		
Williams	1			

SECTION I

About December 20, 1935, a 300 pound hog was butchered by a packing company in central Ohio. The meat was inspected and passed by an inspector. All of the cases to follow in this section ate the pork in a raw state prior to December 25, 1935 except C M who continued to eat it up to January 10, 1936 cooked "very rare."

Case 1 Mr C M, a white male 22 years of age, whose occupation was dairyman, was admitted to University Hospital on January 11, 1936 complaining of generalized malaise, pain in the back, fever and sweating.

Physical examination revealed edema of the eyelids, bilateral conjunctivitis and photophobia. There was marked generalized muscular pain, but other than this the physical examination was essentially negative. His temperature upon admission was 104.2° F, pulse 115, and respirations 38. A blood count revealed hemoglobin 85 per cent, erythrocytes 4,820,000, leukocytes 16,450, 67 segmented, 16 band, 10 lymphocytes, 2 monocytes, and 5 eosinophiles.

Biopsy of the gastrocnemius muscles near the tendinous attachment revealed severe myositis and larvae of *Trichinella spiralis*.

During the course of his stay in the hospital the leukocytes varied between 10,800 and 19,750. The highest eosinophile count was 31 per cent, and it is significant to note that the highest eosinophile counts were noted with the lowest total counts. Agglutination tests for typhoid fever, undulant fever, and tularemia were negative. The cerebro-spinal fluid was normal.

Treatment was symptomatic except for the use of neoarsphenamine which had no apparent effect. The patient was discharged from the hospital February 4, 1936 apparently in good condition except for considerable loss in weight.

Case 2 E B, a white female 27 years of age, was admitted to St Francis Hospital on January 14, 1936 complaining of severe pain in all the extremities, fever, diarrhea, generalized edema and sore throat.

About two weeks previous to admission she had eaten some raw pork and two or three days later first noticed a diarrhea. This continued for several days, and then she became constipated. The patient then developed severe muscular pains in all extremities with accompanying generalized edema, particularly under the eyes. She also had laryngitis which persisted for a few days. No glandular enlargement or swelling, and no vomiting were noted.

The physical examination revealed a white female, acutely ill and prostrated, with marked edema of legs and arms. The skin was anemic, dry and hot. There was marked edema under the eyelids. The throat was much injected and dysphagia pronounced. The heart was normal except for a rapid rate.

On admission her eosinophiles were 70 per cent, and 10 days later, 43 per cent.

Case 3 L E, a white male 30 years of age, was admitted to St Francis Hospital on January 14, 1936. Several weeks previous to admission he had eaten some raw pork. Soon after this he became quite ill and began to have diarrhea. He took a dose of epsom salts, and soon the symptoms began to subside, although edema of the eyelids developed. Diarrhea stopped and constipation was noted. Muscular pains were moderately severe. No nausea, vomiting, or cough.

Physical examination revealed a white male, not acutely ill and in no apparent distress. The skin was negative except for slight redness and edema of the eyelids. Examination was otherwise negative.

On admission his eosinophile count was 33 per cent, 10 days later it was 57 per cent.

Case 4 R B, a white boy eight years of age, was admitted to St Francis Hospital on January 14, 1936. This child ate some raw pork with other members of the family several weeks previous to admission. He became acutely ill, with cramps, diarrhea, and generalized edema. Severe muscular pains were present.

Physical examination revealed a white male child, apparently acutely ill with some evidence of prostration. The skin was negative. The eyes were negative except for slight edema of the eyelids. The examination was otherwise negative.

On admission the patient had 51 per cent eosinophiles, 10 days later they were 20 per cent.

Case 5 M T, a white female 24 years of age, was admitted to St Francis Hospital on January 14, 1936. At this time her temperature was 103° F (rectal) and she complained of pain in the extremities. She gave a history of having eaten raw pork about two weeks previous to her admission to the hospital. Shortly after, she began to develop intestinal symptoms followed by diarrhea. This was soon checked. The patient then developed edema of the eyelids but was relatively free from edema elsewhere. Pains were not particularly severe. She had no nausea or vomiting. She had had a mild fever for two weeks previous to admission.

Physical examination revealed a white female, apparently in no great distress, showing some puffiness of the eyelids. The skin was pale and anemic. The eyelids were slightly edematous with an area of redness around the orbit. Otherwise negative.

On admission she had an eosinophilia of 47 per cent, 10 days later it was 67 per cent.

Case 6 E T, a white female child three years of age, was admitted to St Francis Hospital on January 14, 1936 with pain in the extremities, edema, and fever.

The history was similar to those of the cases above. She developed edema of the eyelids, some diarrhea with occasional vomiting, and a fever of 103° F, rectal.

Physical examination revealed a white female child, acutely ill, and somewhat dehydrated, who apparently had had a high fever for some time. The eyelids showed some evidence of edema. The abdomen was slightly rigid, somewhat tympanic, slightly tender over the spleen and liver. Otherwise negative.

On admission she had an eosinophilia of 21 per cent, 10 days later the count was 32 per cent.

SECTION II

Case 1 C H, a white male 22 years of age, was admitted to University Hospital, January 24, 1936, complaining of swelling of the eyelids, generalized muscular weakness and malaise. The patient gave a history of having eaten improperly cooked hamburgers frequently during the past six months or year. The present symptoms appeared seven days prior to admission. He also complained of nausea, vomiting, diarrhea, and a conjunctivitis. He was seen at the Student Health Service on the campus of Ohio State University and was referred to the hospital with a diagnosis of trichiniasis.

Upon admission the eosinophile count was 72 per cent. His temperature was 102.4° F.

Case 2 G R, a white female 12 years of age (author's case), gave a history of having eaten some rare roast pork (purchased from a chain grocery store) about January 5, 1936, and a day or so afterwards she ate some rare side meat of pork from the same source. About January 14 she first noticed that her eyelids were markedly swollen, especially in the morning. They seemed to recede somewhat at night. On January 16 she began to have cramp-like pains in the muscles of her legs, severe enough to cause her to flex her legs. Extension of the legs was very painful. Her temperature at this time was 102.2° F, pulse 128 and regular. No signs of meningitis were present. A blood count showed an eosinophilia of 31 per cent. A diagnosis of trichiniasis was made. On January 21 calcium gluconate with haliver oil and viosterol was started. The apparent effect of this therapy on the fever encourages us to believe that it may have brought about a shortening of the encystment stage.

CONTROL TESTS

The Bachman skin test was given to a series of patients in St. Francis Hospital who were admitted because of some other disease and who presented no obvious symptoms of trichiniasis. Table 2 shows the results of these control tests. All of the tests were entirely negative except one (L L) which was as strongly positive as any of those obtained in the cases tested in Sections I and II. This patient (L L) gave a history of having eaten raw sausage sandwiches over a period of years and gave a vague history of muscle pains which were believed to be arthritic. She remembered no edema. Her blood count at the time of the test showed 4 per cent of eosinophiles. In view of these findings and her history we regard this as an unrecognized case of trichiniasis discovered by the Bachman test.

COMMENT ON SKIN TESTS

The results from the use of the Bachman test have been quite favorable when used and read correctly. Goldschlager⁵ reports a series of eight cases

all positive to the test. All of his controls were negative except one which he attributes to a phenol sensitivity. Drake,⁶ in a series of 24 cases in which the tests were satisfactorily applied, reports all positive or 100 per cent. In 25 cases that had eaten the infested meat and gave no history of illness but had eosinophilia, only 12 reacted positively to the test, about 50 per cent. McCoy⁹ selected 88 patients that had had the infestation within the past eight years. Of 36 of these who had been ill two to six weeks, 31, or 92 per cent, gave a positive test. Of 39 tested from three to 22 months after infestation, 31 or 80 per cent were found to be positive. Of 13 persons ill three and a half to seven and a half years prior to the test, a total of eight or 62 per cent were positive. He also adds that in 539 tests only seven persons were found to be sensitive to the control injection. Summarizing the above experience (and excluding all cases of McCoy's tested more than six weeks following infestation) the tests were positive in about 95 per cent of the cases.

Our experience with the Bachman test has been very satisfactory. We believe it is as efficient as the average diagnostic skin tests in other fields. We obtained positive reactions in every one of our small series of cases (table 1). The accuracy of the test depends upon securing a suitable preparation of powdered larvae and properly preparing the antigen solution from the powder. At present there is no adequate supply of the material available. New antigen must be prepared frequently. If kept on ice, it is reported to retain its potency for about six months. If not kept on ice it deteriorates much more rapidly. We found one such preparation inert after two months. We believe the commercial production and distribution of powdered trichinella larvae for antigen would be a definite service to the profession.

We did not utilize the Bachman precipitin test⁸ in this study. This test usually does not become positive until three or four weeks after infection. However, it would aid in detecting border-line cases which are of greater duration than this. Bachman,¹⁰ in a report of his work in Puerto Rico, showed that this precipitin test is 90 per cent specific.

CONCLUSIONS

1 Eight cases of trichiniasis with recovery are reported which were all positive to the Bachman intradermal skin test.

2 A résumé of the incidence of the disease in Ohio shows 96 cases in the last eight years with a mortality of 8.33 per cent.

3 The Bachman intradermal skin test is a valuable diagnostic aid in trichiniasis and should supplant the biopsy of muscle.

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CHRONIC ULCERATIVE COLITIS FACTORS INFLUENCING ITS RESPONSE TO SPECIFIC TREATMENT *

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KNOWLEDGE of the condition that is known as "chronic ulcerative colitis" seems to date at least to the "bloody flux" of Sydenham, in 1669

Its bacterial etiology has been recognized only recently. Etiologic significance has generally been ascribed to the diplostreptococcus originally described by one of us

The similarity of this disease, because of its destructive character, to tuberculosis has frequently been emphasized. This fact has made it difficult to evaluate any single therapeutic agent employed in its treatment. Even though many clinicians seem to recognize its similarity to tuberculosis they frequently have not comprehended the importance of a therapeutic regimen similar to that generally accepted for tuberculosis. A carefully regulated and properly organized program of management for this disease cannot be overemphasized. It was with this thought in mind that the study recorded here was undertaken. We have tried to evaluate the part played in this program by our serum therapy or specific therapy.

Two of the major efforts in the treatment of this disease have been to immunize victims of this disease against the diplostreptococcus of colitis and to remove sources distant from the colon that might harbor this organism. Results of cultures of the rectal discharges of these patients have been recorded. An attempt has been made to correlate the incidence of positive culture and the immediate result of treatment.

We have reviewed the cases of chronic ulcerative colitis in which treatment was given during a given period of time to see whether response to treatment varied in the cases in which the diplostreptococcus was found and in those in which the culture of the rectal discharges was reported as negative. Table 1 will illustrate the degree of immediate improvement following our program of management, which included as one of its major efforts the administration of the serum. It will be noted that the patients failed to respond to treatment in only 11 per cent of the cases. These were all cases in which all objective tests lead to the diagnosis of chronic ulcerative colitis or colitis gravis, the type in which the diplostreptococcus is usually found. Grade 1 improvement refers to the group in which there was a slight but unsustained improvement. Grade 2 refers to moderate but continuous improvement, and grade 3 refers to marked improvement with relief of all symptoms and no exacerbation of symptoms up to the time of this review. Grade 4 refers to complete and prompt relief of all symptoms. The latter

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TABLE I

Degree of Improvement in 181 Cases of Chronic Ulcerative Colitis

Culture for Diplo- streptococcus of Colitis	Grade of Immediate Improvement Following Treatment										Total
	0		1		2		3		4		
	Cases		Cases		Cases		Cases		Cases		
	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	
Positive	7	8	9	10	38	43	20	23	14	16	88
Negative	14	15	16	17	35	37	18	20	10	11	93
Total	21	11	25	14	73	40	38	21	24	13	181

group can truly be called healed. A review of this table will promptly suggest that there is no material difference in the response of patients with "positive" cultures and those with "negative" cultures. One might be inclined to infer from this that the improvement which follows treatment is unrelated to the presence of the diplostreptococcus. However, a review of table 2 will promptly dispel such an inference. It will be seen how difficult it is to call a culture "negative" until repeated cultures have been attempted.

TABLE II

Number of Cultures Attempted in 259 Cases before a Positive Culture Was Obtained or a Negative Culture Was Declared

Results of culture	Number of cultures						Number of cultures not analyzed	Total
	1	2	3	4	5	5+		
Positive	86	12	5	2	2	1	35	143
Negative	44	25	19	11	5	12		116

Table 2 presents a review of the number of attempts to culture the rectal discharges of each patient. The number of patients studied in the two series do not correspond in all details because, as would seem obvious, not all patients who have any type of disease can be accurately controlled. The 259 patients represent those who were observed for more than a year.

Table 3 illustrates the amount of bowel involved in a group of 172 cases. The extent of involvement has been graded 1, 2, 3, and 4, corresponding roughly to the four segments of the bowel, that is, involvement, grade 1,

signifies that the process is confined to approximately a fourth of the length of the large bowel. In these cases the involvement was predominantly in the rectum and sigmoid colon, but in a few instances it was only in the cecum and ascending colon or only in the descending or transverse colon. Grade 4 involvement signifies involvement of the entire colon, no special designation being given to those cases (18 in this series) in which roentgenologic examination revealed that there also was involvement of the terminal portion of the ileum.

TABLE III
Relation of Extent of Involvement to Grade of Improvement

Extent of involvement	Grade of improvement										Total	
	0		1		2		3		4			
	Cases		Cases		Cases		Cases		Cases			
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
1	2	4.7	3	7	16	38	15	35	7	16	42	24.4
2	3	19	3	19	4	25	5	31	1	6	16	9
3	1	10	2	20	7	70	0	0	0	0	10	5.8
4	13	12.5	15	14.4	45	43.2	19	18.3	13	12.5	104	60.4
Total	19	11	23	13.4	82	46.5	39	22.7	21	12.2	172	

Study of table 3 reveals that the preponderant percentage of cases (60.4 per cent) falls into the group in which the involvement was grade 4, the others follow in the order 1, 2, and 3. Furthermore, it will be seen that no important relationship can be drawn between extent of involvement and degree of improvement. Patients whose entire colon was involved seemed to respond equally as well to treatment as did those who had involvement of only one segment.

Further study of these cases will reveal that, while the amount of bowel involved has no material relation to the response to treatment, the activity of the disease and the length of time a patient has been ill are definite factors which affect the response to treatment. Even though there is involvement of the entire large intestine, if the degree of activity of the disease is mild, the response to treatment is quicker and more actively sustained, the relief of symptoms is more likely to be complete than if the bowel is involved by more active disease. Obviously, when the disease has lasted for months or years, its continuous onslaught on the bowel will produce damage which may be irreparable. That the length of time the patient has had the disease bears

some relation to the response to treatment is illustrated by table 4. This table would suggest that the benefits to be expected from treatment of chronic ulcerative colitis bear an inverse ratio to the duration of the disease. No one can say just how large a part the administration of serum plays in the therapeutic response in these cases. The fact that relief is frequently dramatic, improvement is rapid, and progressive and complete restoration to normal occurs, suggests that the administration of serum plays a part in the improvement. The fact that improvement is usually slow, even though progressive, would suggest the importance of all the other accessory therapeutic endeavors.

TABLE IV

Relation of Grade of Improvement and the Duration of Symptoms before Treatment

Duration	Grade of Improvement										Total
	0		1		2		3		4		
	Cases		Cases		Cases		Cases		Cases		
	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	Num- ber	Per Cent	
1 year or less	7	11	6	10	20	32	12	19	17	27	62
1 to 5 years	8	10	9	12	37	48	19	25	3	4	76
5 years or more	6	14	9	21	16	38	7	16	4	10	42
Total	21		24		73		38		24		180

This review would further substantiate the opinion previously expressed that surgical interference in these cases should be confined to complications of the disease for many of the patients, even though they make but little immediate response, will in the course of months improve and finally the disease will be completely arrested as far as any intestinal symptoms are concerned.

Another interesting point concerning intestinal disorders was observed during the time that this series of cases of chronic ulcerative colitis was studied. In cases of diarrhea the patients were sent to the laboratory for culture of the stools. Table 5 illustrates the number of these cases in which the diplostreptococcus was found, but in which there was no objective evidence of chronic ulcerative colitis. These cases represent only a very small fraction of the cases of diarrhea in which cultures for this organism were made during the period of this study. Several of the patients in these cases passed blood later during an attack of acute pharyngitis. Others who had an irritable colon improved as a result of the administration of anticolitis

vaccine Others experienced an attack of diarrhea following the administration of too large a dose of the vaccine These observations would suggest a subclinical condition of colitis and would suggest the nature of treatment advisable in selected cases of this type

TABLE V

Cases in Which the *Diplostreptococcus* Was Present without Objective Evidence of Chronic Ulcerative Colitis

Final Diagnosis	Cases
Irritable colon	16
Deficiency diarrhea	3
Subacute purulent appendicitis	1
Typhoid fever	1
Amebic dysentery	1
Diverticulosis	1
Tuberculous enteritis	1
Rectal abscess	1
Chronic infectious arthritis	1
Simple diarrhea	1

SUMMARY

The importance of a well-ordered program of treatment in cases of chronic ulcerative colitis cannot be overemphasized When all objective tests point to a diagnosis of chronic ulcerative colitis, even though positive cultures for the *diplostreptococcus* are not obtained, specific treatment should be given The number of attempts which should be made to culture rectal discharges and to culture the lesions directly through the proctoscope remains unsettled In many cases in which the culture is reported "negative" on first culture, the culture will become "positive" on repeated cultures This fact emphasizes the difficulties of making cultures of the stools and the importance of following details of a well-ordered technic

Response to treatment varies inversely with duration of the disease and directly with its activity and severity Patients who harbor the *diplostreptococcus* of colitis and who have diarrhea, even though they have no proctoscopic evidence of the disease, may be saved much trouble by undergoing treatment for subclinical types of colitis

FURTHER OBSERVATIONS ON RAPID HYPOSENSITIZATION¹

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RECENT textbooks on allergy make only little mention of rapid hyposensitization[†] treatment and only a few clinicians have given this method serious consideration. The method of administering small increasing doses of antigen at short intervals was first introduced by Besredka¹ for the avoidance of serum reactions after he had observed that in animals the re-injection of a sublethal dose of antigen resulted in a temporary state of anti-anaphylaxis and that during this state larger doses of antigen could be more readily tolerated.

In 1930 Freeman² adopted this method of treatment for the relief of patients with hay-fever and asthma. His case reports, however, rather tend to discourage its application for clinical use. He was forced to add epinephrine to each injection because of the occurrence of severe constitutional reactions, yet, in spite of this precaution such reactions occurred. Tuft³ and Blankenhorn³ reported cases of shock and death following injections of horse serum in patients in whom desensitization had been attempted by giving increasing doses at short intervals.

For some time past, we have attempted to adapt this method to clinical application in allergic patients suffering from asthma and hay-fever. At first we met with little success because of the frequency of severe reactions. In a preliminary report⁴ we concluded that this procedure was not devoid of danger. Our interest was greatly stimulated after we had begun to use co-seasonal treatment for hay-fever and asthma. This mode of treatment taught us two principles which we found to be the key to any form of hyposensitization, namely, to start with a sufficiently small dose and to gauge the dose of subsequent injections from the size of the local wheal obtained on the site of the previous one.

INDICATIONS

With co-seasonal treatment, we found as have Vaughan,⁵ Phillips⁵ and others that prompt relief from hay-fever can be established in many instances. The beneficial results, however, are often transient and in the severe cases inadequate (especially is this true in pollen asthma). If more lasting results are to be obtained it is essential to reach a higher final dose.

* Received for publication January 25, 1937.

† The term "hyposensitization" is used by some in order to indicate that "complete" desensitization, as in an anaphylactic animal, is impossible in man. We do not believe that such a distinction is possible since in man no one has ever given, for the purpose of desensitization, doses corresponding even approximately to those given to an anaphylactic animal per kilogram of body weight. However, we shall adhere to the common nomenclature to avoid confusion.

Recent experience has convinced us that in severe chronic asthma in which the causative antigens are known this is the method of choice. Another main indication for this treatment exists in patients with hay-fever or asthma in whom the time for treatment is limited. It has also proved successful in cases of atopic eczema of known etiology. In cases of marked multiple sensitivity in which the diet was greatly restricted, it has been of great value to us in the effort to counteract sensitization to those antigens which were most important in keeping up the patient's nutritional state. We are particularly referring to rapid hyposensitization against such foods as milk, wheat and egg. Although we have only a limited experience with the prevention of "allergic" shock following therapeutic or prophylactic injections of animal serum, we believe that the principles advocated here are applicable to any form of serum therapy.

TECHNIC

Our technic is as follows. The initial dose should be such that the resulting wheal from the injection will have subsided within 45 minutes. This can be accomplished if we use, for example, a dose as low as $\frac{1}{2}$ Noon unit (0.0005 mg.) of pollen extract, in an average pollen case. In the more sensitive individuals this dose is reduced, in the less sensitive ones as high as 3 units (0.003 mg.) to 5 units (0.005 mg.) are given as the initial dose. This infers, of course, that the patient has actually been found to be sensitive to the specific antigen and that a larger dose will produce the usual local reaction. As a guide we routinely perform scratch tests at first. Should they be markedly positive (as in case 2, in which a scratch test with ragweed extract produced a generalized reaction), we repeat the tests after an interval of 15 to 20 minutes in order to establish local wheals repeatedly. After having thus produced moderate sized wheals one can more easily build up the first intradermal doses. As antigens we employed mostly pollen but also any of the other inhalants, foods, and other substances which we felt, by skin tests and clinical evidence, were of primary importance. We frequently used combinations of various antigens. No different therapeutic response was noted whether the injection was given intradermally or subcutaneously. The intradermal injections, however, because of the more distinct appearance of the wheal, were of greater service as a gauge for further treatment.

If the preliminary injections result in no, or little local whealing the subsequent ones may be given at very short intervals (10 to 15 minutes) and the increase may be from 50 to 200 per cent of the previous dose. After the desired wheal is obtained, the injections must be increased more slowly (from 10 to 30 per cent of the previous dose) and the intervals made longer (from 2 to 6 hours). If no swelling is obtained upon the rapid increase of doses and frequent injections the case should be re-investigated and search for other antigens be made.

If too large a swelling occurs or if an aggravation of the existing symptoms takes place, the treatment should be discontinued for 6 to 8 hours and then renewed with lower doses

REACTIONS

Marked local edema at the site of injection may be indicative not only of an early reaction, if it appears rapidly, but also of a delayed "allergic" reaction. This may occur six to ten hours after the treatment had been administered. If an early constitutional reaction is encountered, we give no, or very little epinephrine ($\frac{1}{20}$ to $\frac{1}{10}$ c c) as the use of epinephrine may mislead us in gauging the doses for the subsequent treatment. This is in contrast to the technic advocated by Freeman who administered epinephrine frequently together with the antigenic extract. After a generalized reaction has occurred we discontinue the injections for a given period and decrease the subsequent doses. In such a case it is sometimes desirable to stop the treatment for a whole day and to continue with smaller doses without a subsequent immediate increase.

In "intravenous" or "backseepage" reactions (Waldbott and Ascher⁶) which are evidenced by their immediate onset (within 10 seconds to a few minutes) and occasionally by bleeding upon the site of injection, epinephrine is, of course, indicated in large doses.

As a rule we do not set ourselves a definite goal as to the final dose. In the effort to reach too high a dose one may produce constitutional reactions and thus defeat the purpose of the treatment, namely, immediate improvement. We do, however, often reach a final dose as high as is customary in hyposensitization treatment.

RESULTS

In discussing the results obtained, two questions should be dealt with separately. Firstly, is it possible to reach safely large doses in a relatively short period of time? Secondly, how does the improvement resulting from this treatment compare with that attained by other methods? Chart 1 presents data bearing on the first point from a group of seven consecutive cases and indicates that within a period of four to seven days, doses as high as 8000 units of pollen extract can be reached without untoward effect. It should be emphasized that all the cases included here were found definitely sensitive to the antigens administered. Even in cases in which constitutional reactions occurred relatively large doses could be reached as seen in chart 2.

In comparing end results with those obtained by other methods the question of proper controls is very complicated. Practically anything may "cure" an asthmatic at any time. Especially in the chronic asthmatic such measures as hospitalization, discontinuance of epinephrine or other drugs and such natural means of relief as the termination of a pollen season, of

a fungi season, of an infection, etc., may contribute to or induce a "cure" Furthermore, a patient apparently "cured" for a considerable period of time may at any time under certain circumstances have a flare-up of the previous disease merely because of an unusually heavy exposure to antigens to which a latent sensitivity may exist That previously positive skin reac-

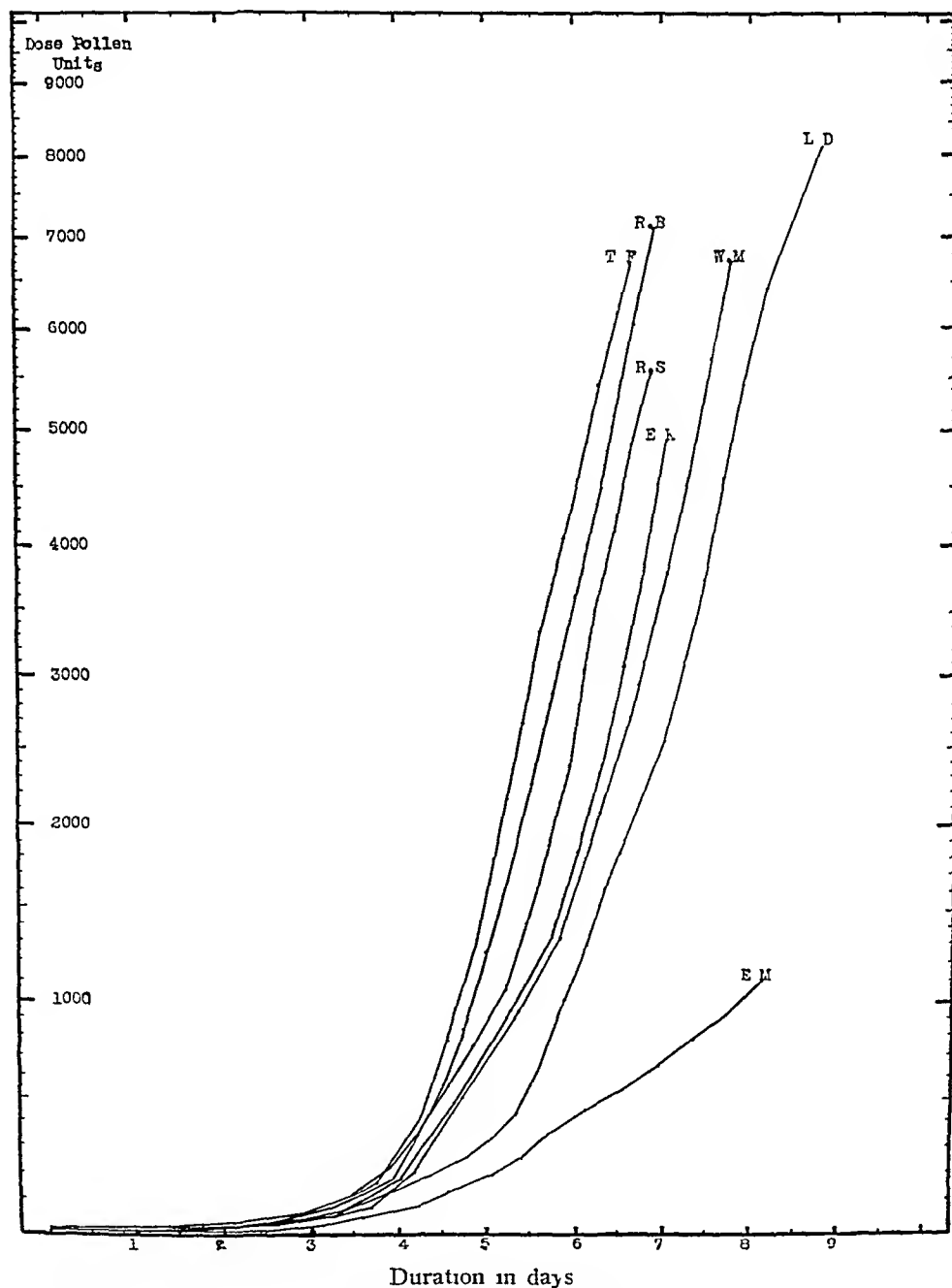


Chart 1 demonstrates how relatively high doses of extract can be reached in a short time in seven consecutive pollen cases

tions become negative after administration of antigen at 'short intervals was recently shown by Rackemann and Wagner'. This, however, again cannot be considered a criterion of a "cure". To speak of a "percentage of cure," as it is often done, particularly in connection with hay-fever therapy, is again subject to the above objections

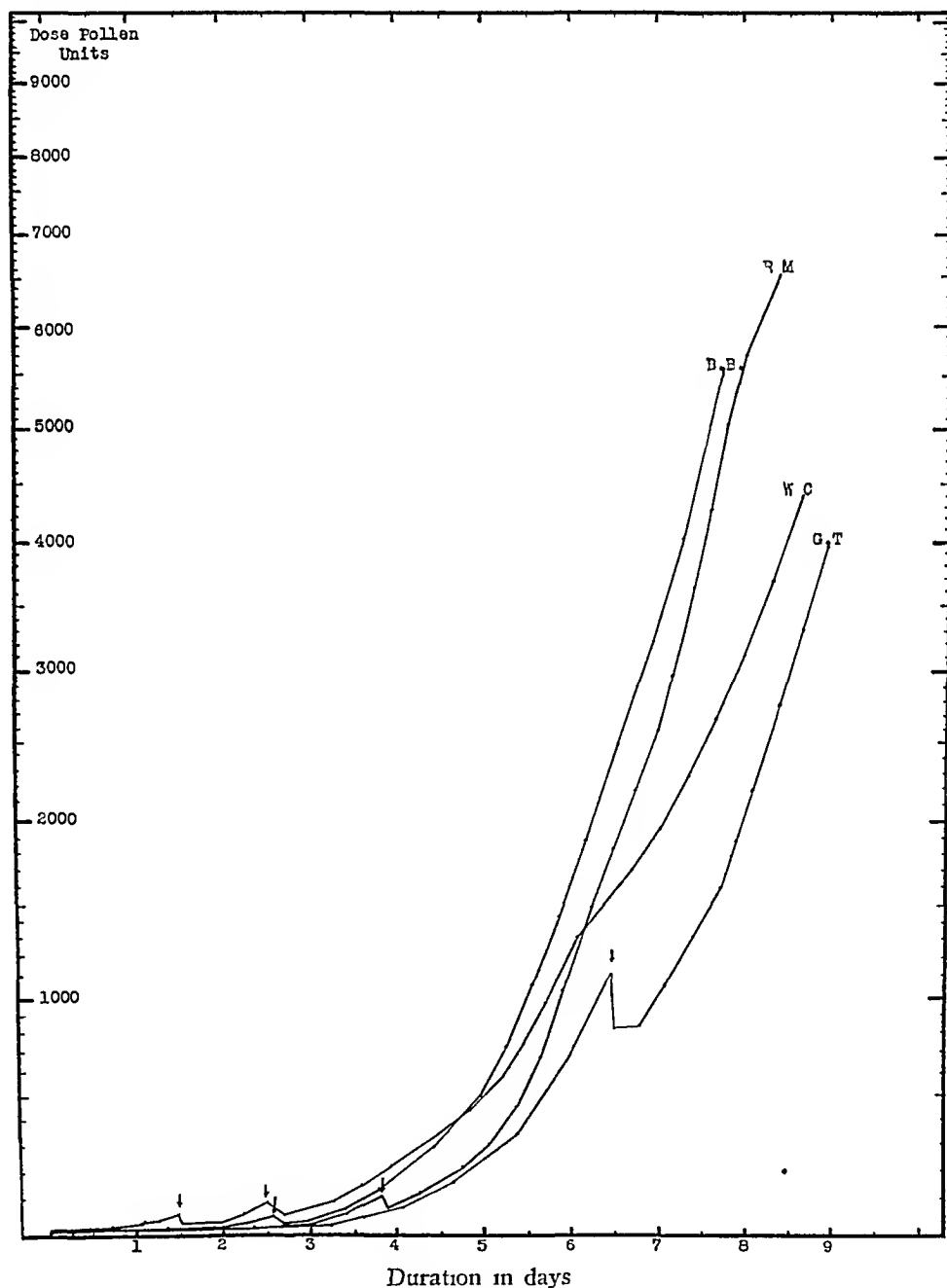


Chart 2 demonstrates the increase in doses following constitutional reactions in four selected pollen cases

Conforming with the purpose and the indications of this method of treatment and the difficulties involved in establishing adequate methods of control, we therefore do not concern ourselves with the late effects of this treatment, but are merely recording the clinical improvement, i e, the relief of symptoms noticeable during a period of several weeks. In the pollen cases of this series this period of time extended throughout the respective pollen season. All our patients were instructed to return to the office or to notify us immediately upon the return of any symptoms at any time. A recent follow-up on the cases included here, assured us that this instruction had been carried out and reaffirmed our previous opinion.

The treatment had been administered to more than 300 patients. Of these we selected 146 in whom we felt that as adequate a control as possible had been established. We are referring here to the discontinuance of other therapeutic measures, to the lack of success with such measures, to the length of time during which the patients had been under our observation before and after the treatment, as well as to the general trend of allergic symptoms as influenced by the climatic condition of the respective season. In these patients we, furthermore, had evidence to believe that the antigens used were the primary causative agents.

Among these 146 cases, there were 78 with hay-fever, 61 with asthma, or asthma combined with hay-fever, 7 with atopic eczema. Fifty-two became entirely free from symptoms, the improvement becoming noticeable immediately after the first few injections. 83 patients were considerably improved, 11 failed to respond to the treatment. Among the 83 patients who were "considerably improved," 21 had what we considered to be late reactions, which were evidenced by a temporary aggravation and which were followed by subsequent freedom from symptoms. With our advancing experience the number of these reactions has been reduced. Most of the asthmatics had been in a rather severe asthmatic state. Thirty-nine out of the 61 had to be hospitalized. Of these 39, only four failed to show definite improvement.

The following are the protocols of three representative cases.

CASE REPORTS

Case 1 Mrs. F. B., aged 46, was admitted to Grace Hospital on June 4, 1936 at the height of the grass pollen season with a severe attack of bronchial asthma. She had been treated by such measures as epinephrine, $\frac{1}{8}$ to 1 c c, eight times a day, opiates, barbiturates, inhalation of stramonium powders, iodides by mouth and intravenously, and, at intervals of two to three days, injections with various antigenic substances to which she had shown positive reactions. In spite of this therapy the asthmatic state persisted. On the tenth day of admission all medication was discontinued. As no improvement took place during the two following days, 1 Noon Unit (0.001 mg.) of a combination of grass pollens (Orchard Grass, June Grass, Red Top, and Timothy) was given intradermally, after preliminary scratch testing had shown two to four plus reactions to these pollens. Subsequent injections with a moderate increase were given at three hourly intervals so that a dose as large as 4500 units (4.5

mg) was reached on the fourth day. After the third injection there was a definite subsidence of the asthmatic symptoms. She was discharged from the hospital on the eighteenth day and remained under our observation for two more months, free from asthma.

Comment This patient represents a typical instance in which hospitalization and other methods failed. Here a rather high dose of antigen was reached within a short time, giving prompt and lasting relief.

Case 2 Miss I. D., aged 35, was seen in a severe asthmatic state on September 2, 1933, having had perennial allergic asthma for 18 years. The patient had previously shown a marked sensitivity to the common pollens, epidermals and to a large number of foods. On checking the dermal tests a marked generalized reaction was encountered within one minute after the application of a drop of concentrated extract of short ragweed upon the scarified skin. According to the patient's statement a similar experience had occurred previously when she was given an injection of $\frac{1}{10}$ Noon unit (0.0001 mg.) of ragweed pollen intradermally. Being aware of this sensitivity we endeavored to produce frequent local wheals without injections, namely, by applying a drop of ragweed extract for a graduated period of time upon the scarified skin and washing it off at first after one second, then three seconds, then eight seconds, etc., at intervals of from one-half to two hours judging the time interval from the size of the local wheal produced. At the end of the second day the patient could tolerate the extract on the scarified skin for 20 minutes without producing a generalized reaction. A marked local edema had ensued after each application. On the third day it was possible to inject a dose of $\frac{1}{50}$ unit (0.00002 mg.) ragweed pollen, this was followed up at intervals of two hours by $\frac{1}{33}$ unit (0.00003 mg.), $\frac{1}{20}$ unit (0.00005 mg.), $\frac{1}{100}$ unit (0.00008 mg.). On the sixth day 150 units (15 mg.) was reached. Upon the second application of the extract to the skin the asthmatic condition distinctly improved. Soon after the first intradermal injection the patient became free from asthma with the exception of slight attacks at night, which subsided entirely after two more days, in spite of the fact that the ragweed pollen season had not yet been terminated.

Comment In this case an unusually marked degree of sensitivity was combated by rapid hyposensitization treatment. The production of local wheals either by scratch or subcutaneous application of the antigen must have been instrumental in bringing about prompt relief. While unquestionably various other antigens were contributing to this patient's asthmatic condition, the control of what appeared to be the principal reactor at that time, we believe, aborted the attack.

Case 3 Miss T. F., 52 years old, had had severe attacks of asthma during the past 10 years lasting as a rule from late May to the middle of October. Two sisters had also been suffering from allergic asthma. On skin testing positive reactions to the grass pollens, the ragweeds, orris root, wheat and egg were obtained. Admitted to the Charles Goodwin Jennings Hospital on August 11, 1936, with severe asthma, she was treated with a combination of antigenic extracts 1 to 4 units (0.001 to 0.004 mg.) of pollen in conjunction with epinephrine, ephedrine, barbiturates. The condition became progressively worse. In addition to 4 to 6 daily doses of epinephrine, opiates, calcium, iodides, oxygen and glucose intravenously were resorted to. On the fourth day of admission when the patient was seen by one of us (G. L. W.) all medication was discontinued except for $\frac{1}{10}$ or $\frac{1}{20}$ c.c., of 1:1000 epinephrine given

about two to four times in 24 hours. This resulted in no change of the severe asthmatic state. The following morning the patient was placed on a rapid hyposensitization regime starting with an initial dose of $\frac{1}{10}$ unit (0.0001 mg) of pollen extract with a very slight increase of doses at hourly intervals. The first five injections did not cause local swelling. When a slight wheal was obtained with the sixth dose, 2 units (0.002 mg), a decided improvement was noted. However, the asthma did not completely subside. For the following injections another extract was employed with which no more wheals were obtained in spite of a rather marked increase in doses (It was determined later that this extract had not been made up in the usual manner and was of very little potency). The asthma recurred and became gradually worse until the patient again was in a critical condition. An intramuscular injection of 50 c.c. of serum from a patient recovered from pollen asthma was of no avail. Assuming that the lack of response to the treatment might be due to the insufficient potency of the extract it was replaced, without the patient's knowledge, by the one previously used. The initial dose $\frac{1}{10}$ of 1 unit (0.0001 mg) produced a wheal of about $2\frac{1}{2}$ cm in diameter with pseudopods. Relief was noted after 20 minutes. Subsequent treatments were given at intervals of one to three hours. Although the doses were increased only very slightly, local reactions occurred after each injection. On August 23 a dose of 80 units (0.8 mg) was reached. The patient was discharged from the hospital a few days afterwards.

Comment This represents another patient with severe asthma in a critical state in whom various therapeutic measures had failed. Here again, the improvement coincided with the production of local reactions by the antigen. The failure to elicit such reactions apparently resulted in a relapse. An impotent extract accounted for this fact. It is noteworthy that the dose of 0.1 unit failed at first to elicit a local reaction while after four days, it resulted in definite wheals.

CONCLUSIONS

1 Rapid hyposensitization, we believe, deserves a definite place in the treatment of allergic diseases. Particularly in the severe asthmatic in whom the causative antigens are known, it has proved to us to be the method of choice.

2 Successful treatment by this method is dependent on the administration of the proper antigen or combination of antigens, i.e., those which form the patient's dominant sensitivity.

3 The danger of causing constitutional reactions or of aggravating existing symptoms can be obviated if one abides by the following principles:

a The initial dose should be sufficiently low so as not to produce much local swelling.

b The doses and intervals between treatments should be carefully gauged for each individual injection, the principal guide being the degree of local edema which is produced by the previous one.

c An incipient constitutional reaction which may merely manifest itself by a temporary aggravation of existing symptoms should be recognized and carefully guarded against by a readjustment of the proposed schedule of treatment.

d No epinephrine, or as little as possible, should be used in conjunction with the treatment in order not to interfere with the production of a local swelling

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THE THERAPEUTIC USE OF VENESECTION IN POLYCYTHEMIA

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ALTHOUGH venesection has been used for many years as an emergency measure in erythremia, its general use as a therapeutic agent in this disease has been considered contraindicated on the grounds that reduction of the blood level by this means would act as a further stimulus to erythrocyte production¹ Recent investigations, however, have indicated that this assumption may be unwarranted Falconer² has shown that the repeated removal of from 200 to 600 c c of blood at intervals of from a few days to three weeks did not increase the reticulocyte percentage above normal limits Reimann and Breuer³ have studied the effects of systematic venesection in seven patients with polycythemia vera Reduction in the red blood cell and hemoglobin level was accomplished by repeated bleeding over a period of several weeks The resulting symptomatic and hematologic remissions were maintained for an average period of two years without further treatment Detailed studies of the effect of venesection on the various other hematologic and circulatory abnormalities characteristically found in polycythemia have not been encountered in the literature

This communication reports the results of a study of the therapeutic effect of venesection in the treatment of five cases of erythremia in whom the use of phenylhydrazine was considered inadvisable because of age or a history of previous vascular thrombosis⁴ In addition to clinical observations and determination of the red blood cell and hemoglobin levels and the reticulocyte percentage, studies of the hematocrit, blood volume, blood viscosity and, in some instances, circulation time and oxygen saturation of the arterial blood were made before, during and after periods of bleeding Two (R R and A G) of the five patients studied presented the characteristic picture of polycythemia vera, without demonstrable cause for the high hemoglobin and red blood cell levels Patients M M and M P have also been considered instances of polycythemia vera, although cardiac lesions, which may have led to some degree of anoxemia, were demonstrable, both exhibited splenomegaly and increased blood volume, usually not observed in the "secondary" types of polycythemia The polycythemia of patient S W was apparently secondary to pulmonary fibrosis

METHODS

Venesection was accomplished either by the multiple syringe method or by the withdrawal of blood through a large needle into a flask under negative

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pressure induced by suction. As a rule, 500 c c of blood were withdrawn at intervals of from one to three days until the desired red blood cell, hemoglobin or hematocrit level was reached. In general, an attempt was made to reduce the hematocrit to a normal or slightly subnormal value. Red blood cell and white blood cell counts were estimated with the use of pipettes and counting chambers certified by the U S Bureau of Standards. For each red blood cell determination the average of two counts made in the usual manner was taken. Hemoglobin values were estimated in the Sahli hemoglobinometer, frequently calibrated by oxygen capacity. Reticulocyte counts

S.W. # 47306

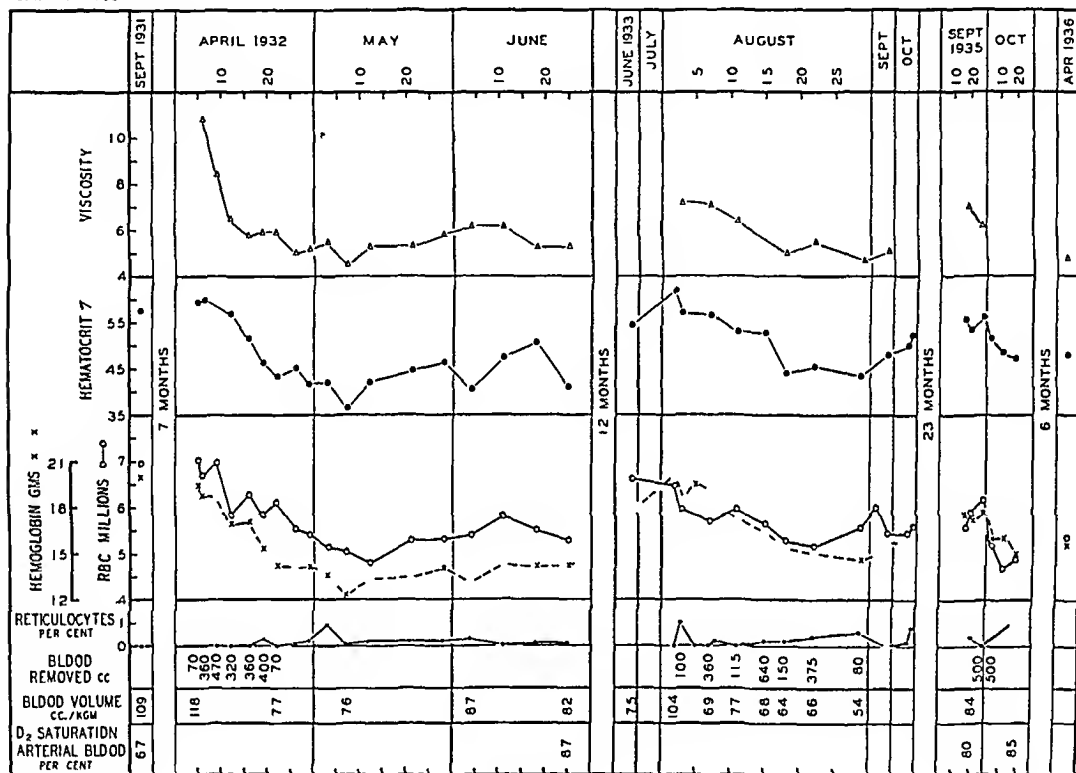


FIG 1

were made in "wet" preparations, stained with cresyl blue, 1,000 cells were counted for each determination. The relative volume of the red blood cells was determined by the Wintrobe hematocrit method⁵. Blood viscosity was determined by means of the Hess viscosimeter at 100m temperature. Blood velocity was determined as the arm to tongue circulation time by the Decholin method*. The blood volume was estimated by the method of Keith, Rowntree and Geraghty,⁶ as modified by Hooper, Smith, Belt and Whipple⁷. We have some doubt as to whether the values obtained for blood volume in the presence of a high hematocrit value represent a close approximation of the actual volume of circulating blood when determined by this method. There

* The decholin-sodium used in these experiments was generously supplied by the Riedel de Haen, Inc

is reason to believe that complete mixing of the dye may not occur in the time interval allowed to elapse between the injection of the dye and removal of the sample for determination of the dye content of the plasma, because of the marked increase of the blood viscosity and slowing of blood flow. The values obtained are probably lower than the actual blood volume. Although there may be some doubt as to the reliability of the absolute values

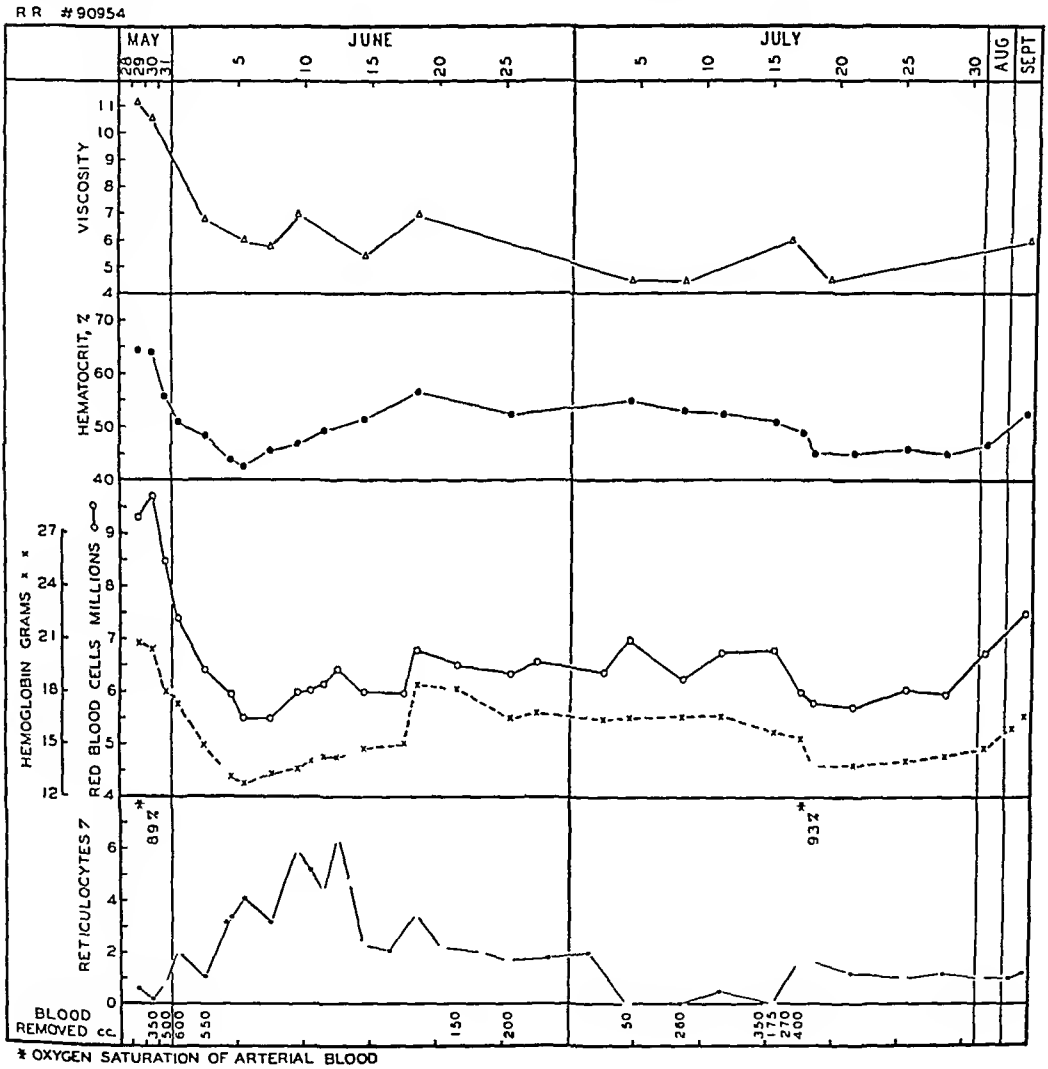


FIG 2

obtained in the presence of a high hematocrit and increased blood viscosity, a comparison of the effect of therapy on the blood volume estimations is of interest and some significance

The following case reports are supplemented by summaries of hematologic observations presented in figures 1 to 4 and table 1. Some of the earlier observations in case 1 were made by Drs S H Bassett and A Hurtado in connection with studies of the iron balance

M P #92221

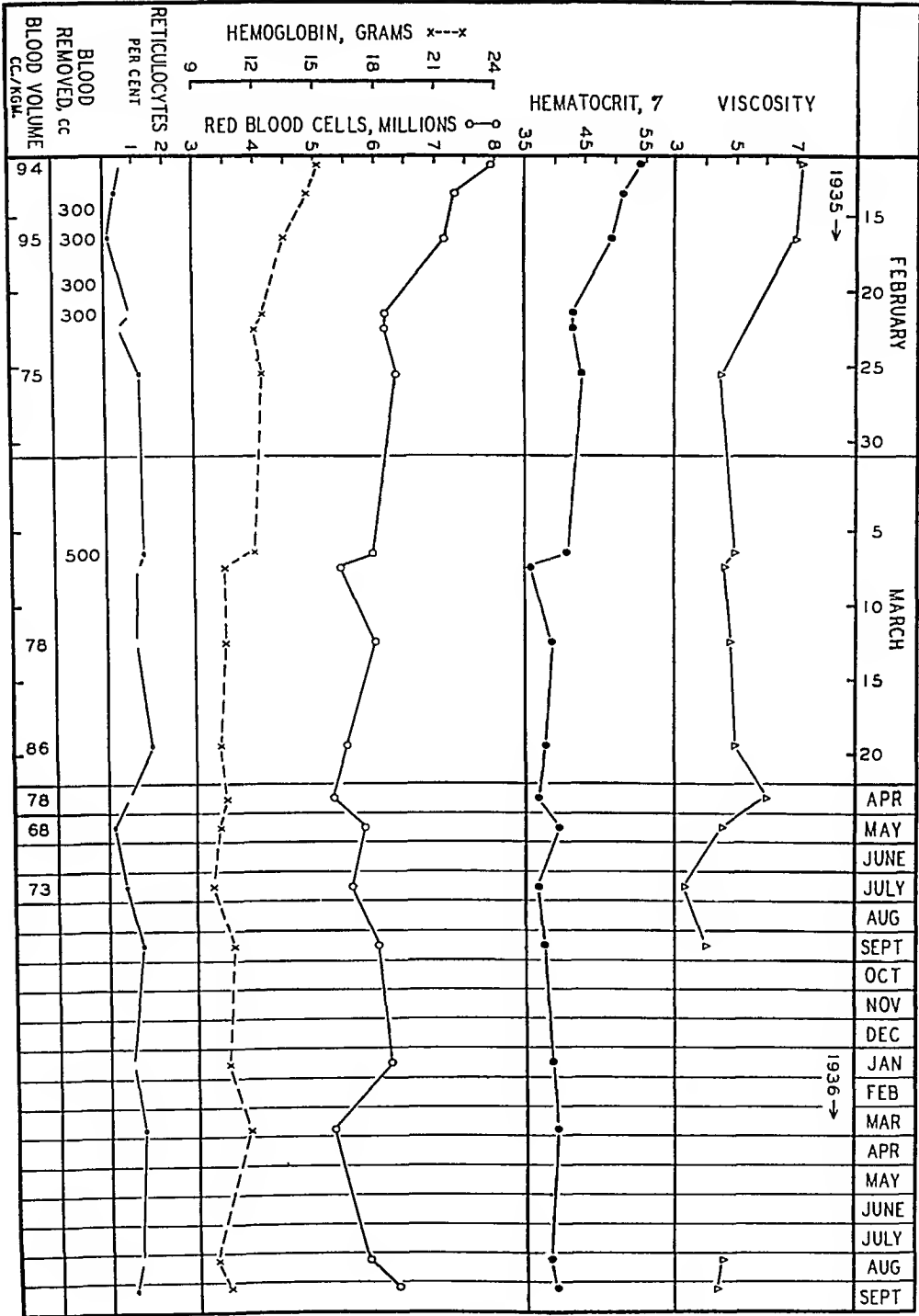


FIG 3

A.G. #38999

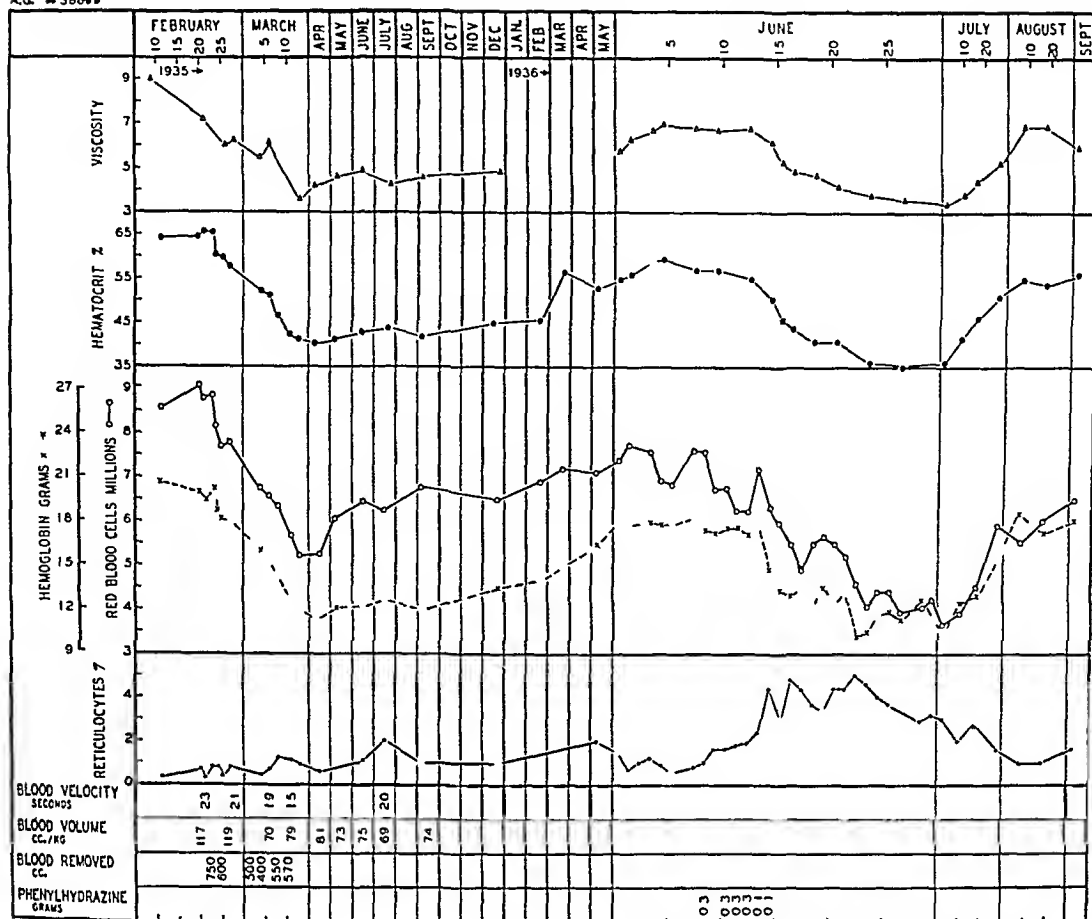


FIG 4

TABLE I

Subject	Date	R B C Millions	Hgb Grams	Hematocrit Per cent	Mean Corpuscular Volume Cubic Microns	Mean Corpuscular Hemoglobin $\gamma\gamma$	Remarks
A G	2-20-35	9.08	19.8	64.8	71.4	21.6	Before venesection
	3-11-35	5.68	12.0	42.5	74.6	21.1	After venesection
	12-28-35	6.53	13.5	45.0	68.6	20.6	9 months after venesection
	6-2-36	7.74	17.9	56.0	72.4	23.1	15 months after venesection
	7-2-36	3.66	10.5	36.0	98.2	28.2	2 weeks after phenylhydrazine
	8-18-36	6.07	17.3	54.0	89.0	28.5	8 weeks after phenylhydrazine
M M	4-1-33	7.08	19.9	66.0	93.2	26.2	Before treatment
	4-30-33	4.77	12.2	40.0	84.0	25.6	2 weeks after phenylhydrazine
	9-22-33	6.80	18.9	61.0	88.4	27.8	4 months after phenylhydrazine
	10-3-33	6.15	15.7	53.0	86.6	25.2	After venesection
	12-5-33	5.96	15.0	50.7	85.1	25.2	After venesection
	1-29-35	5.82	18.6	60.5	104.0	32.0	After phenylhydrazine for one year
	10-15-35	4.94	12.3	41.0	83.0	24.9	1 month after venesection
	5-26-36	5.60	15.5	45.0	80.3	27.7	8 months after venesection

CASE REPORTS

Case 1 S W, a 56 year old foundry worker, was admitted to the hospital on May 12, 1931 complaining of shortness of breath, "purplish color of the skin" and smothering sensation under the sternum of one year's duration. About six weeks before admission these symptoms became more intense. On admission the patient was orthopneic, and the respirations and pulse were rapid. The mucous membranes and nail beds were deeply cyanosed. The retinal veins were engorged and the neck veins greatly distended. Moderately coarse râles were scattered throughout the entire chest. The heart was markedly enlarged to the left. The liver was enlarged, but the spleen was not felt. There was pitting edema over the lower extremities.

The blood findings were as follows: red blood cells 7,300,000 per cu mm, hemoglobin 19.5 grams per 100 cc, hematocrit 67.7 per cent and white blood cells 11,600 per cu mm. The electrocardiograph showed right axis deviation. Roentgenogram of the chest revealed the heart to be greatly increased in all of its diameters. The pulmonary fields showed diffuse, fine reticular fibrosis, in addition to soft mottling and feathering over the lower fields. The vital capacity was 650 cc.

The patient was treated by venesection (1,000 cc) and oxygen inhalation and on discharge one month later was much improved.

The patient was next seen in September 1931 and April 1932, at which time he was again dyspneic and orthopneic at rest. The pertinent findings in reference to the blood are shown in figure 1. With the removal of a total of 2,100 cc of blood, the red blood cell count, hemoglobin, hematocrit, blood volume and viscosity fell to slightly below the average values for normal individuals. There was no appreciable increase in the reticulocyte percentage. The oxygen saturation of the arterial blood rose from 67 to 87 per cent. When the patient was discharged from the hospital on June 27, 1932, his cardiac compensation was good for moderate activity and dyspnea was considerably ameliorated.

Twelve months later, the patient was again seen because of recent increase in dyspnea. The blood findings are given in figure 1 and show that there was again a marked increase in the red blood cell and hemoglobin level. After a series of venesections the level was again reduced to the normal zone where it remained for approximately two years. It is significant that none of the periods of bleeding in this patient were followed by any increase in the reticulocytes.

Case 2 R R, a 40 year old brewmaster, was seen in this clinic in June 1934, because of a hematoma of the left thigh which had appeared following a fall. At this time the spleen was not felt and the red blood cell and hemoglobin levels were within normal limits.

In May 1935, the patient was readmitted to the hospital because of inability to talk and use the right arm and leg. For several weeks his wife had noted that the face and hands were becoming increasingly red and dusky. Examination revealed a red discoloration of the skin, particularly noticeable on the face, neck, hands and mucous membranes. The retinal veins were engorged and there was a small retinal hemorrhage lateral to the left disc. The spleen was palpable two fingers-breadth below the costal margin. Neurological examination showed right facial weakness and complete paralysis of the right arm and leg. Details of the examination of the blood are given in figure 2. In addition to these, the white blood cell count was 36,400 per cu mm and the icterus index, 32.

During a period of 5 days a total of 2,000 cc of blood was removed by venesection. Immediately after venesection the serum proteins were decreased to 4.4 grams per cent. This period of venesection was followed by an increase in the reticulocyte to 6.3 per cent.

Six weeks later, because of an increase in the blood counts (figure 2), an addi-

tional 1,200 c c of blood were removed This was followed by a maximum reticulocyte response of only 17 per cent

After the patient was discharged in July 1935, approximately 3,000 c c of blood were removed over a period of a year There has been partial improvement in the paralysis and dysarthria and he has remained free of further symptoms referable to polycythemia The spleen has not been palpable during the past year Blood studies obtained in October 1936 through the courtesy of the patient's physician, Dr C B F Gibbs, were as follows Red blood cells 6,130,000, hemoglobin 9.2 grams per 100 c c, hematocrit 31 per cent, reticulocytes 0.8 per cent, white blood cells 16,600, icterus index 8 and blood viscosity 3.6 From July 1935 to October 1936 the mean corpuscular volume fell from 76 to 51 cubic microns and the mean corpuscular hemoglobin from 24 to 15 micromicrograms

Case 3 M P, a 56 year old housewife, complained of dull aching pain in the left upper abdomen of two years' duration During the past several months she had noted progressive enlargement of a mass in the left upper abdomen In addition there had been dizziness and faintness occurring frequently during the past few months and sensations of burning of the feet There had been several recent epistaxes In childhood she had had rheumatic fever and since the age of 25, until the past two years, she had had seasonal hay fever and asthma, occurring in the autumn At the age of 50, she had experienced an episode of severe precordial pain, accompanied by prostration and collapse Since that time she had taken digitalis regularly

In February 1935 physical examination showed a dusky violaceous discoloration of the face, neck and hands The mucous membranes were deep red in color The retinal veins were engorged The heart was enlarged to the left and to the right, the pulmonary second sound was accentuated A loud, rough, systolic murmur was transmitted from the apical region to the axilla The spleen was markedly enlarged, extending downward to the iliac crest The liver edge was palpable three fingers-breadth below the costal margin

The blood findings are given in detail in figure 3 Other pertinent findings were White blood cells 14,100 per cu mm with a normal differential count, mean corpuscular volume 69 cubic microns, mean corpuscular hemoglobin 19 micromicrograms Electrocardiographic tracing showed right axis deviation Roentgenogram of the chest showed increased linear markings with fine feathering of both pulmonary fields The heart was enlarged in all of its diameters

Between February 15 and March 7 a total of 1,700 c c of blood was removed by venesection Reduction of the red blood cell count was followed by symptomatic improvement and a slight reduction in the mean corpuscular volume and hemoglobin and in the size of the spleen During and after the period of bleeding there was no significant change in the white blood cell count or the differential count

After discharge from the hospital digitalis was continued in maintenance dosage Up to the present time, 20 months after venesection, there has been no significant change in the blood picture and there have been no symptoms referable to polycythemia The spleen has remained at about the same size as when discharged from the hospital Following venesection, this patient has maintained a mild degree of hypochromic, microcytic anemia without symptoms and without evidence of hemolysis or of excess red blood cell regeneration

Case 4 A G, a 55 year old housewife, was first seen in this clinic in 1930 at which time a diagnosis of duodenal ulcer was made Examination of the blood showed no abnormalities at that time The red blood cell count was 5,500,000 per cu mm, hemoglobin 14.2 grams per 100 c c

The patient was admitted to the hospital in February 1935, complaining of frequent dizzy spells and increased color of the face and hands of several months' duration On examination deep red color of the face and hands was noted The retinal

veins were dilated. The heart and lungs were negative. The lower border of the spleen was felt five fingers-breadth below the costal margin. The liver edge was at the costal margin. The left foot and the lower left leg were cyanotic and swollen, apparently due to thrombosis of the deep veins of the leg.

Laboratory data in addition to those charted in figure 4 revealed an oxygen saturation of the arterial blood of 94 per cent, icterus index of 8, and a white blood cell count of 9,800 per cu mm with a normal differential count. Roentgenogram of the chest showed no pulmonary or cardiac abnormalities.

During a period of 14 days a total of 3,370 c.c. of blood was removed by repeated venesection. The maximum reticulocyte count during and after the period of bleeding was 12 per cent. At the time of discharge from the hospital the abdominal symptoms, the dizziness, faintness and the pain in the left foot had disappeared. The spleen decreased in size so that it was no longer palpable.

The patient was observed at intervals in the Out-Patient Department. The symptomatic and hematologic remission induced by venesection continued for approximately one year. In February 1936 occasional dizziness was experienced, during the next four months the frequency of the attacks increased and there was a gradual rise in the number of red blood cells. The spleen again became palpable two fingers-breadth below the costal margin. In June 1936 it was decided to observe the effect of a course of phenylhydrazine for comparison with the effect of venesection. During the period of hemolysis the reticulocytes increased to 48 per cent, mild jaundice appeared and was accompanied by an increase in the icterus index to 30. During the period of blood destruction the serum proteins increased from 6.3 to 7.2 grams per cent and the white blood cell count from 6,450 to 21,100 per cu mm with some increase in the percentage of neutrophils, no immature white or red blood cells appeared in the peripheral blood. The white blood cell count and differential count, the icterus index and the serum protein returned to pre-treatment levels within three weeks after discontinuance of the administration of the drug. The dizziness disappeared with the reduction in the blood level, but there was no significant change in the size of the spleen. Within two months the red blood cell count had risen to the pre-treatment level (figure 4) and symptoms had returned. A second course of treatment with this drug was given with similar results. In this patient the administration of phenylhydrazine was accompanied on both occasions by marked increase in ulcer symptoms, so that she refused to take a maintenance dose of the drug.

Case 5 M. M., a 40 year old stenographer, was admitted to the hospital in April 1933 complaining of fainting and dizzy spells of six years' duration. Her complexion had always been ruddy, but during recent years the bluish red color of her face, neck and hands had increased. There was a history of frequent epistaxes. In childhood she had had scarlet fever, chorea and poliomyelitis. At the age of 24 right salpingectomy and oophorectomy was done and at 27 she had peritonitis following an abortion. At 34 thyroidectomy was performed.

Physical examination showed bright, bluish red color of the face, neck, upper chest, hands and legs. There was slight exophthalmos and the retinal veins were engorged. The area of cardiac dullness was enlarged to the left, there was a pre-systolic thrill at the apical area, with systolic and presystolic murmurs. Blood pressure 160 systolic, 100 diastolic. The spleen was palpable three fingers-breadth below the left costal margin.

The hematologic picture is shown in table 1. The white blood cell count was 7,900 per cu mm. Differential count was as follows: neutrophils 58 per cent, lymphocytes 24 per cent, monocytes 5 per cent, eosinophiles 10 per cent and basophiles 3 per cent. Roentgenogram of the chest showed prominent linear pulmonary markings and cardiac enlargement. The electrocardiogram was normal.

During a period of 14 days, the patient received a total of 18 grams of phenyl-

hydrazine hydrochloride Two weeks later the blood level was slightly below normal (table 1) The viscosity of the blood fell from 15 to 6 and the blood volume from 91 c c to 72 c c per kilogram of body weight Following the administration of the drug the symptoms were ameliorated Within two months, in spite of the administration of small doses of the drug, the symptoms began to increase and the blood level began to rise

She was readmitted to the hospital in September 1933 because of a convulsive seizure The blood viscosity was 17 During a period of two months 2,000 c c of blood were removed by six venesections The maximum reticulocyte response during this period was 20 per cent

In February 1934 the red blood cell count was again elevated and phenylhydrazine (10 gram) was again given This course of the drug was followed by thrombosis of the left dorsalis pedis artery During the following 18 months the patient was followed at frequent intervals in the Out-Patient Department, receiving a total of 76 grams of phenylhydrazine in doses varying from 0.1 to 0.3 gram per week During this time there was progressive increase in the hemoglobin, hematocrit, viscosity and the mean corpuscular volume, although there was little change in the number of red blood cells (see table 1 under date 1/29/35) At this time the patient was having frequent fainting episodes and complained of tingling of the fingers In March 1935 after an epistaxis, which resulted in the loss of an estimated pint of blood, these symptoms became less severe

In April 1935 the removal of 1,500 c c of blood resulted in a hematologic remission of four months' duration It is of interest that on this occasion venesection was followed by an increase in the reticulocytes to 62 per cent In September 1935 the erythrocyte count had increased to such a level that 1,500 c c of blood were removed, again resulting in a decrease in the blood level to slightly less than normal (table 1) The maximum reticulocyte response following venesection on this occasion was only 20 per cent During the following eight months there was a slight rise in the red blood cell and hemoglobin values

In this patient there was only partial correlation between the blood level and the presence of fainting episodes, which were in many ways suggestive of petit mal seizures The changes in the size and hemoglobin content of the red blood cells following the use of venesection and phenylhydrazine were of particular interest and will be discussed

RESULTS

By means of repeated and systematic venesection at intervals of from one to several days it was possible to reduce the relative volume of the red blood cells to a normal or slightly subnormal level There was a corresponding decrease in red blood cells and hemoglobin and reduction in the blood viscosity, blood volume and blood velocity to approximately normal levels In two subjects, the oxygen saturation of the arterial blood was increased following venesection Hematologic improvement was usually accompanied by marked relief of symptoms referable to the polycythemia, and by reduction in the size of the spleen The characteristic "red" cyanosis disappeared and there were evidences of improvement in the capillary and venous circulation as the blood level was lowered The reticulocyte response to bleeding was of particular interest because of its significance as an index of erythropoietic activity Nine of the eleven periods of bleeding were followed by no significant increase in the percentage of reticulocytes It may

be of significance that the two periods of venesection which were followed by reticulocyte increases followed periods of blood destruction. In the case of patient M M the period of bleeding which was accompanied by a reticulocytosis of 62 per cent followed the prolonged administration of phenylhydrazine. Patient R R, when first seen, was jaundiced, with an icterus index of 32, interpreted as evidence of previous blood destruction. Four of the five patients experienced symptomatic and hematologic remissions of from eight months' to two years' duration without further treatment. Remissions of shorter duration were observed only in those patients who exhibited a reticulocyte response to venesection and who presumably had abundant stores of iron and other blood-building materials as the result of previous blood destruction.

Unfavorable reactions to venesection were not encountered, even when large amounts of blood were withdrawn within a period of a few days. No evidences of stimulation of the white blood cell or platelet elements of the bone marrow were observed. A temporary decrease in the level of the serum proteins was noted for a few days after the withdrawal of large amounts of blood but no clinical manifestations of serum protein deficiency appeared.

In one patient detailed observations of the effect of both venesection and phenylhydrazine are available (patient A G, figure 4). Satisfactory reduction in the red blood cells, hemoglobin, hematocrit and blood viscosity, and temporary relief of symptoms were accomplished by the administration of a relatively small dose of phenylhydrazine hydrochloride. In comparing the effect of the two therapeutic procedures in this patient, at least two significant and probably related observations are noteworthy. First, the administration of phenylhydrazine was followed by a reticulocytosis not observed after venesection. Second, the remission induced by phenylhydrazine was of less than two months' duration, as contrasted with a remission of 15 months' duration following venesection. As a result of the gastrointestinal symptoms which accompanied the administration of phenylhydrazine, this patient insists on returning to the use of venesection when further treatment of the polycythemia becomes necessary.

It is of interest that three of the five patients exhibited microcytosis and hypochromia of the red blood cells of significant grade. In two patients observations of the red blood cell size and hemoglobin content after treatment with both phenylhydrazine and venesection are available (table 1). In the case of patient A G, there was no significant change in the microcytosis and hypochromia during the 15 months' remission which followed venesection. The administration of phenylhydrazine, however, was followed within a relatively short period of time, by a consistent and significant increase in the cell size and hemoglobin content. Patient M M originally presented red blood cells which were normal in size and hemoglobin content. No significant change was observed after a single course of phenylhydrazine,

followed by a period of venesection. The administration of phenylhydrazine in maintenance doses during a period of one year, however, resulted in a significant increase in the mean corpuscular volume and hemoglobin. Although the number of red blood cells per cubic millimeter showed but little change during this period, the increase in erythrocyte size was sufficient to result in a gradual increase in the hematocrit, hemoglobin and blood viscosity, with coincident increase in the severity of symptoms. The removal of a total of 3,000 c.c. of blood by repeated venesection was followed by a significant reduction in the cell size and hemoglobin content.

DISCUSSION

The syndrome of erythremia is characterized by a marked hyperplasia of the bone marrow, as a result of which characteristic increases in the red blood cell count, hemoglobin, hematocrit, blood viscosity and blood volume occur. The symptoms of the disease result for the most part from the plethora and stasis of blood flow due to the marked increase in blood volume and the overfilling of the vascular tree, especially in the capillary bed. Splenomegaly is usually present. Phlebitis and vascular thromboses are common.

Although the primary lesion is in the bone marrow, there has been no unanimity of opinion as to the etiology of the pathologic increase in erythropoietic activity. There are those who have felt that the increased activity of the bone marrow is malignant in nature and analogous to the disordered cell activity which occurs in leukemia. Others have been impressed with the probable relationship of polycythemia to anoxemia, which is generally recognized as a powerful stimulant of erythropoietic activity. The "secondary" polycythemia observed in patients with cardiac and pulmonary lesions and the polycythemia encountered at high altitude would seem to be best explained on this basis. Further evidence of the probable importance of anoxemia has recently been provided by the studies of Reznikoff, Foot and Bethea.⁸ These authors observed distinct capillary thickening and subintimal and adventitial fibrosis of subarteriolar capillaries, arterioles and arteries of the bone marrow of seven patients with polycythemia vera. They raise the question whether the anoxemic state caused by vascular disease in the bone marrow itself may be responsible for the excess red blood cell production, particularly in those patients without obvious lesions in other viscera which might lead to anoxemia. With such an explanation of the bone marrow overactivity in so-called polycythemia vera, the erythremia and symptomatology of both types of polycythemia may be reasonably regarded as an overcompensatory response of the bone marrow to lowered oxygen tension. Even in those types of polycythemia in which the increase in red blood cells seems to be in response to an increased demand for oxygen-carrying material, the circulatory disturbances resulting from the increased blood viscosity and slowing of the blood flow may increase the difficulty in

oxygen exchange Under these circumstances the advantage gained by increase in hemoglobin may be more than offset by the disadvantage of circulatory embarrassment due to the increased corpuscular mass In such instances of "secondary" polycythemia, as well as in polycythemia vera, symptomatic improvement follows relief of the circulatory embarrassment by reduction in the number of erythrocytes by means of appropriate therapeutic measures

Of the various therapeutic procedures recommended for the treatment of erythremia, phenylhydrazine has been most extensively used and its effects most thoroughly studied Satisfactory hematologic and symptomatic remissions have been induced by means of this agent in a large number of reported cases Brown and Giffin⁹ have shown that reduction in the red blood cell count and hemoglobin is accompanied by reduction in the hematocrit, blood viscosity and blood volume and by improvement in circulatory efficiency Although the effect of a single course of phenylhydrazine is of relatively short duration, remissions may be prolonged by the continued administration of a suitable maintenance dose of the drug, the size of which must be individually determined A number of patients have been described in whom satisfactory remissions have been maintained for periods of many years¹⁰ Although the large majority of patients with polycythemia apparently may be satisfactorily controlled by the use of phenylhydrazine preparations, the use of this drug has certain practical as well as theoretical disadvantages The amount of the drug required to produce the desired effect varies widely from patient to patient Due to its cumulative and delayed action, the degree of hemolysis produced may be difficult to predict and control Instances of severe and even fatal anemia have been observed following its use in polycythemia Giffin and Conner⁴ state that it should be used with extreme caution, if at all, in elderly patients and in those in whom thromboses have been observed or suspected

The effect of phenylhydrazine on the blood and the bone marrow has been extensively studied in the experimental animal as well as in the patient with polycythemia Hemolysis is accompanied by the appearance of jaundice, increase in circulating bilirubin and increase in the urinary excretion of bile pigments and porphyrins Blood destruction induced by phenylhydrazine, however, results in no increase in the excretion of iron, which is retained and stored in the various organs, particularly the spleen and liver¹¹ It is apparent, therefore, that iron and perhaps other blood building materials, liberated by the hemolytic action of phenylhydrazine, are retained in the body for future use in erythropoiesis The use of the drug in polycythemia is usually followed by a marked leukocytosis, frequently with the appearance of immature myeloid elements in the peripheral blood Thrombocytosis also usually occurs and is thought to be responsible for the peripheral thromboses occasionally observed after the administration of phenylhydrazine Observations in humans, as well as in animals, have shown that phenylhydrazine, either directly or indirectly through its hemolytic action, is

a powerful bone marrow stimulant, resulting in proliferation of erythroid, myeloid and platelet elements of the bone marrow. The reduction in the red blood cell count is usually accompanied by reticulocytosis, leukocytosis and thrombocytosis, interpreted as evidence of increased bone marrow activity. The administration of phenylhydrazine to animals may be followed by the appearance of nucleated erythrocytes and immature myeloid cells in the spleen, liver and other organs.¹² Harrop¹ has suggested that intensive treatment with phenylhydrazine, radiation or venesection may be responsible for the leukemoid changes observed in some cases of polycythemia. It appears that, although phenylhydrazine, due to its hemolytic action, is capable of controlling the symptoms and peripheral blood picture of erythremia, its effect on the bone marrow may accentuate the existing marrow hyperplasia and may lead, through continued stimulation, to the appearance of leukemoid changes simulating myeloid leukemia.

Although there is a considerable literature dealing with the use of roentgen therapy in polycythemia, the effects of its use in this disease have not been extensively studied. Symptomatic improvement and reduction in the red blood cell and hemoglobin levels may follow irradiation of the spleen or long bones. Some students of the disease feel that roentgen therapy is the safest and most effective form of therapy available.¹

Recent reports have suggested the use of solution of potassium arsenite¹⁰ and repeated aspiration of the gastric contents¹³ in the treatment of polycythemia. The usefulness of these measures remains to be determined.

Objections to the general use of venesection in the treatment of polycythemia have been limited almost entirely to the assertion that it would result in increased stimulation of an already active bone marrow. This statement is apparently based primarily on observations of the results of hemorrhage in individuals with previously normal blood levels and on the result of bleeding experiments in animals. The degree of bone marrow stimulation observed under such conditions, however, appears to depend on several factors. Among these are the amount of blood lost, the resulting degree of anemia and the availability of iron and other blood building materials. The removal of as much as 500 c.c. of blood from a normal individual is followed by no reticulocyte response. However, the anemia occurring in humans after a large hemorrhage is followed by reticulocytosis and rapid regeneration of blood, provided adequate stores of iron and other blood building materials are available. It is significant that in those patients whose iron stores have been depleted by means of chronic blood loss, reticulocytosis and other evidences of blood regeneration do not appear until adequate amounts of iron are provided.¹⁴ Direct evidence that blood withdrawal results in increased bone marrow activity in erythremia is apparently limited to occasional observations of rapid red blood cell regeneration after reduction to anemic levels following a large hemorrhage. Our observations, as well as those of Falconer² and of Reimann and Breuer³ indicate that, in polycythemia, the use of venesection under controlled conditions is

not ordinarily accompanied by evidences of increased bone marrow activity. In this regard, it should be noted that only a slight, if any, degree of anemia is produced and that the withdrawal of the large amounts of blood necessary to reduce the hematocrit to a normal or slightly subnormal level results in the removal from the body of relatively large amounts of iron and other blood building materials. The prolonged remissions which follow reduction of the blood level by this means and the absence of reticulocyte response are interpreted as evidence that bleeding under these conditions may not result in significant increase in erythropoietic activity.

Venesection is a relatively simple procedure, the effects of which may be accurately controlled. Its use is apparently not attended by many of the dangers and undesirable side effects of phenylhydrazine and roentgen therapy. Its advantages and relative freedom of disadvantages would appear to warrant its more extensive use in the treatment of polycythemia, particularly, for the present at least, in those patients in whom the more orthodox therapeutic measures seem to be contraindicated or inadvisable.

A consideration of the erythrocyte characteristics in polycythemia, particularly in relation to the iron metabolism and the effect of therapeutic procedures is of interest. Hurtado¹⁵ noted that the polycythemia observed in natives living at high altitudes was characterized by a red blood cell which was larger, contained less hemoglobin and was less saturated with oxygen than the erythrocyte of normal subjects living at sea level. A marked increase in the hematocrit was observed, although the average number of grams of hemoglobin per 100 cc of blood had approximately the same value as the normal average at sea level. The corpuscular volume and the corpuscular hemoglobin varied inversely with the level of the red cell count, so that the hemoglobin concentration was found to be remarkably constant at approximately 25 per cent, considerably below the average normal of 34 per cent at sea level. These observations suggested that the adaptation processes to high altitude, from the point of view of blood morphology, were to be found not primarily in red cell and hemoglobin increases but rather in a close correlation between the cell number, volume and hemoglobin content and in the existence of a larger surface area in a given volume of blood and in the individual erythrocyte for the hemoglobin and oxygen content.

Similar studies of erythrocyte characteristics apparently have not been made in other types of polycythemia. It is usually stated that the size and diameter of the erythrocytes in polycythemia are normal,¹⁶ although the color index is nearly always decreased. In three of the five patients here reported, the mean corpuscular volume and hemoglobin content were well below the lower limits of normal and in one of these (R. R.) were further decreased after repeated venesection. In two instances (table 1) the cell size and hemoglobin content increased after the administration of phenylhydrazine, decreased following venesection. The microcytosis and hypochromia observed in these patients were similar to the changes which take

place in the erythrocytes in the iron deficiency anemias, suggesting that in at least some patients with polycythemia a relative iron deficiency may result from the increased demand for blood-building materials

A decrease in the average volume of the red blood cells in polycythemia should be physiologically advantageous, since the increased blood volume and blood viscosity, which are responsible for the stasis and slowing of blood flow, are due to the elevated hematocrit. The level of the latter is determined not only by the number of red blood cells per cu mm but also to a large extent by the mean corpuscular volume. Recent studies of the anemias¹⁶ have indicated that the size, volume and hemoglobin content of the erythrocytes are determined by the relative amounts of stroma and hemoglobin-building substances, particularly iron, which are available. If it may be assumed that, in the presence of adequate stroma-building material, the level of erythrocyte production in polycythemia is determined by the stimulating effect of anoxemia, then the size of the red blood cells delivered to the peripheral circulation should depend on the amount of iron available for hemoglobin construction. A comparison of the effects of phenylhydrazine and venesection appears to support this hypothesis. It has already been noted that the large amounts of iron resulting from hemolysis induced by phenylhydrazine, are stored in the body for future use. The therapeutic use of venesection, on the other hand, removes from the body large amounts of iron and other erythrocyte building-materials, which are then no longer available for the resynthesis of hemoglobin. Reimann and Breuer³ stressed the apparent importance of this factor and felt that it was chiefly responsible for the good results observed in their patients. It is of interest that in five of their seven cases the color index was decreased after venesection.

The observations in patient R. R. indicate that the repeated withdrawal of large amounts of blood may, in time, result in a blood picture similar to that observed in chlorosis and in the iron deficiency anemias. Such an occurrence should not be considered a contraindication to the therapeutic use of venesection for the control of the polycythemic state. If considered advisable, the cell size and hemoglobin content may be increased by the administration of suitable amounts of iron.

SUMMARY

The therapeutic use of venesection has been studied in five patients with polycythemia.

Reduction of the elevated hematocrit values to a normal or slightly subnormal level by means of systematic venesection was accompanied by comparable reduction in red blood cells, hemoglobin, blood viscosity and blood volume and by improvement in circulatory efficiency. The symptomatic and hematologic remissions so induced were maintained for relatively long periods without further treatment. Venesection was followed by increases in the reticulocyte percentage only in those instances in which the tissue

stores of iron were presumably increased as a result of previous blood destruction

The prolonged remissions and absence of reticulocyte increases following reduction of the blood level indicate that venesection under these conditions does not result in significant increase in erythropoietic activity. The relatively long duration of the symptomatic and hematologic remissions observed after venesection is thought to be due to the fact that removal of the large amounts of blood required to produce the desired effect results in the loss from the body of considerable amounts of iron and other potential blood building materials. In several instances decrease in erythrocyte size and hemoglobin content was observed after periods of bleeding.

Systematic venesection appears to be a relatively safe and efficient therapeutic procedure, which compares favorably with other measures used in the treatment of polycythemia.

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CASE REPORTS

PERIARTERITIS NODOSA WITH A CASE REPORT

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Diffuse vascular lesions with bizarre clinical symptoms of general systemic infection have been reported under various names both in this country and abroad. Because the majority of these cases, unfortunately, have not been diagnosed during the course of the illness, it is apparent that one should keep in mind the possibility of periarteritis nodosa in patients with indefinite symptoms of infection without known etiology and in which all the laboratory studies throw no light on the case.

As one of these, we wish to present the following case of periarteritis nodosa which was missed clinically and even on gross postmortem examination. The final diagnosis was arrived at only after careful study of microscopical sections.

CASE REPORT

Mrs. L. W. (aged 64) was first seen April 12, 1936 with a chief complaint of pain in the legs for the preceding two months. The pain was bilateral, below the knees, especially on the left, cramp-like in character, located in the area of the gastrocnemius, present only when the legs were dependent, and always disappearing when the legs were elevated. There was no change in the color or temperature of the skin. Symptoms referable to the various systems were negative, except for "asthmatic influenza" last winter which kept the patient in bed for three weeks. Examination revealed an aged, white, decrepit female. Skin was dry. Pupils were equal and reacted to light and in accommodation. Ears, nose, throat, heart, lungs, and abdomen were negative. The blood pressure was 158 systolic and 80 diastolic. The extremities were normal in color and their color did not change with changes in position. There was a normal palpable pulsation of the popliteal and dorsalis pedis arteries. There were several varicose veins that filled with dependency and emptied with elevation. Reflexes were entirely normal. The clinical impression at this time was that the pain was circulatory in nature, and due probably to inadequate venous return. On April 13, 1936, the red blood cell count was 3,900,000, white blood cell count 14,350, hemoglobin 55 per cent, polymorphonuclear leukocytes 84 per cent and lymphocytes 16 per cent. The red blood cells were large and irregularly-shaped. The urine was acid, showed no albumin or sugar, and the microscopic examination showed a few pus cells with an occasional granular cast. The patient at this time was put on iron medication (ferrous sulphate) and advised to wear bandages on both legs.

For two weeks, with the bandages, there was no leg pain. On May 2, 1936, however, she began to feel remarkably weak and developed pain and numbness from the elbow to the finger tips of the right hand. This lasted two days. The temperature was 98° F. Examination of the arm revealed nothing abnormal, the heart was found normal and the general examination gave negative findings. The patient was

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put on large doses of yeast with the possibility in mind of a vitamin B deficiency. She felt fairly well for four days, and then, in addition to the great weakness, she showed an inability to walk. She was seen again on May 8, 1936, and at this time complained of sharp shooting pain in both legs, despite the bandages which had been worn constantly. The temperature at this time was 102° F. The tongue for the

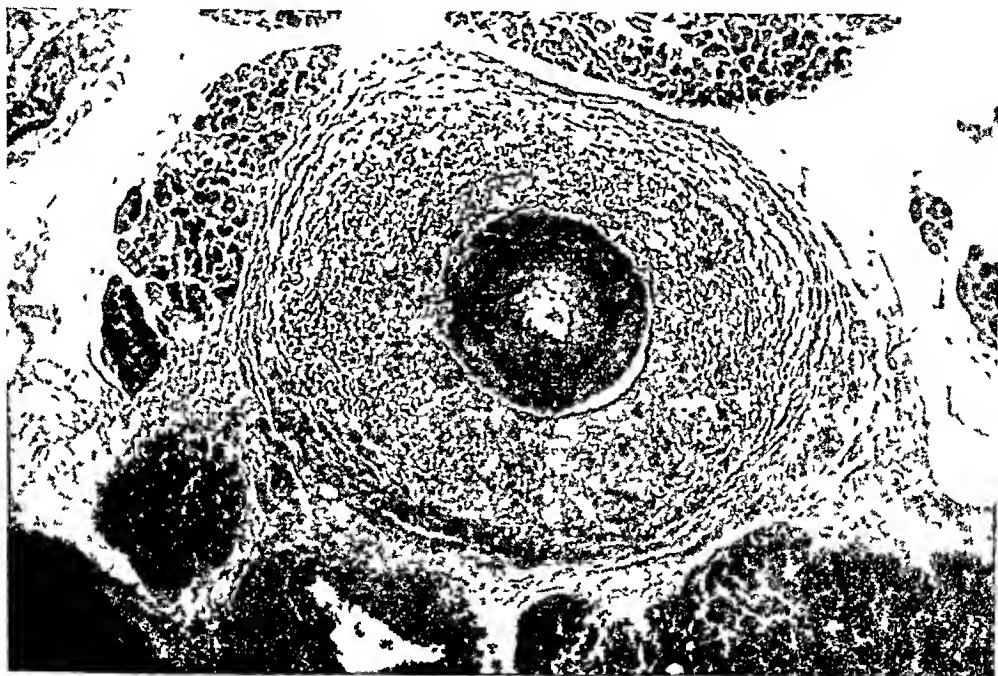


FIG 1 Medium sized artery of the pancreas showing thrombosis and canalization. Marked hypertrophy and leukocytic infiltration throughout the layers and intimal degeneration (100 X)

first time was smooth, red and painful. Physical examination otherwise was negative. On May 9, 1936, temperature was still 102°, in addition to the glossitis, there was noted for the first time altered sensation including vibratory sense in both legs with bilateral foot drop. The arms were normal both symptomatically and objectively.

The patient was admitted to Montefiore Hospital on May 10, 1936 with a provisional diagnosis of nutritional anemia, possibly pernicious anemia. On May 11, 1936 she developed tingling and sharp shooting pain in the right arm and two days later in the left arm. Both became progressively worse until there was complete loss of use with disappearance of position sense, pain and thermal sensation, and bilateral wrist drop. The temperature was 101° F, pulse 120, and blood pressure 160 systolic and 90 diastolic. Significant findings were mainly neurological. The tongue was smooth and red. There were diminished reflexes in the upper extremities and absent reflexes of the lower extremities, motor weakness in all extremities especially in the right arm, and atrophy of the hands. There was loss of vibratory and position sense of the lower extremities. Neurological diagnosis, in view of the history and laboratory findings, was posterolateral sclerosis, and the patient was put on liver by mouth and parenterally.

Laboratory findings confused rather than clarified the picture. The blood Wassermann and Kahn were negative, and the spinal fluid examination was negative. Gastric analysis showed hypochlorhydria. The urine showed a trace of albumin, occasional hyaline casts, and 4 to 6 pus cells per field. The blood non-protein nitrogen

was 40 mg per cent. Examination of the urine for heavy metals was negative. On admission the blood examinations showed 63 per cent hemoglobin, 3,430,000 red blood cells, 16,250 white blood cells, and 91 per cent polymorphonuclear leukocytes. Reticulocytes remained less than 1 per cent in spite of therapy, the red cells appeared microcytic and there was no stippling. The blood count did not change materially during the stay in the hospital. Roentgenologic examination of the digestive tract showed no abnormalities.



FIG 2 Arteriole (section of the liver) showing complete obliteration of the lumen, perivascular infiltration with leukocytes. Fibrosis and hyaline degeneration of the media (100 X)

Throughout the patient's three week stay in the hospital the neurological findings did not change. The blood picture remained the same despite liver, vitamin B, HCl, iron, and transfusion of 300 c c of blood on three occasions. The major complaint was weakness, and this became progressively more severe. On May 27, the patient had a brief syncopal attack characterized mainly by severe abdominal pain and dizziness while lying quietly in bed. This did not recur. There were daily rises of temperature to 101°, the pulse running constantly between 100 and 120. The patient left the hospital on June 2, 1936 still not definitely diagnosed, the diagnosis of toxic polyneuritis, cause unknown, being retained for want of something better.

At home the patient became progressively worse. She continued to complain of marked weakness, and the neurological picture remained unchanged. Physical examination otherwise remained negative, except for a few rales in both bases. The blood pressure was 180 systolic and 100 diastolic. On June 3, patient began to vomit all food and liquids, lost her voice, and became distended. This continued until June 6, when she died.

Autopsy performed several hours later showed on gross examination an extremely emaciated white adult female about 65 years of age, with marked pallor of the skin and mucous membranes. Superficial glands were not palpable. Abdomen was flat and no palpable tumors were present. The extremities showed marked

atrophic changes of the extensor muscles and thenar and hypothenar eminences of the palms. The abdominal organs were found in normal positions and relations. Patchy discolorations were present in the walls of the ileum and jejunum. Mesenteric lymph nodes were enlarged. The mesentery was studded with minute yellow gray nodules, firm in consistency. Several of these were visible on the serous covering of the



FIG 3 Showing blood vessels of the kidney. The smaller vessels are involved in an inflammatory reaction while the large sized vessels are free from such reaction (50 X)

bowels. No masses were found. The stomach and large bowel were distended with gas. The liver weighed 1200 grams, had a thick fibrotic capsule, and on cut surface showed mottling of gray areas on a purplish-red background. The spleen was twice normal size, had a thickened capsule, and on cut surface showed marked interstitial fibrosis. The kidneys were atrophic and sclerotic with coarse granulation of the cortex. The adrenals appeared normal. The lungs disclosed old pleuritic adhesions with fibrosis and calcification of both apices. There was edema and congestion of the bases. The heart was pale with flabby myocardium. Excessive subepicardial fat was present. The valves were intact. The coronaries were free from arteriosclerotic changes, though discrete atheromatous patches were seen in the intima of the aorta. The meninges were slightly injected and the cerebral vessels were free from arteriosclerotic changes. There was moderate edema of the brain, but no neoplasm or hemorrhage. The spinal cord showed no gross lesions. The gross anatomical diagnoses were: Marked anemia, chronic myocardial degeneration, congestion and edema of lungs, chronic mesenteric lymphadenitis, ileitis, septic splenitis, edema of brain, bilateral symmetrical atrophy of the upper and lower extremities, and chronic perihepatitis.

Relevant microscopical examination showed marked inflammatory and degenerative changes of medium sized arteries and arterioles in the following organs: liver, kidneys, pancreas, mesentery and spleen. The brain, heart, lungs and adrenals were free from such changes. The nature of the inflammation consisted of several stages of the same process. Some involved the adventitia with marked perivascular infiltration of polymorphonuclear cells. Others involved both the media and adventitia, while in the third group, all three layers were involved with hyaline degeneration, thickening of intima and media with obliteration of the lumen and areas of aneurysmal

dilatation. Sections of the spinal cord did not reveal any cause for neurologic changes in the extremities. Histological diagnoses were periarteritis nodosa of visceral vessels, chronic myocardial degeneration, edema of brain, and chronic nephritis.



FIG 4 Arteriole from mesenteric branches showing marked narrowing of the lumen due to hypertrophy and hyalinization of the intima. Fibrosis of the media and some perivascular infiltration. (50 X)

DISCUSSION

In a review of the literature, the terminology for this condition is found to differ slightly with various authors: periarteritis nodosa, polyarteritis acuta nodosa, and panarteritis. The first description was published in 1865 by Kussmaul and Maier who named the disease periarteritis nodosa and stated that it consisted of inflammatory changes around the adventitia of small arteries and arterioles resulting in multiple nodules along the course of the vessels. Later, Dickson,¹ in 1908, after summing up the literature, differentiated the lesions under two headings. One group was caused by syphilis and was called periarteritis nodosa, while the second group was caused by some unknown infection or toxin and was called polyarteritis acuta nodosa.

As to etiology, Mott and Barton believe that the disease is a luetic manifestation which involves small arteries frequently including the coronaries and occasionally the cerebral vessels. Derick and Hass' report² contains an interesting discussion of the etiology of this disease in which they doubt that periarteritis nodosa is a separate entity at all and believe, in view of their case, that the syphilitic virus is most likely the cause of the arteritis. Their case was one of arteritis of syphilitic origin in a young adult which was diagnosed only after microscopic study of the lesions. They found inflammatory lesions of the small arteries with involvement of all the layers and of periaarteriolar tissues, many vessels showing partial or complete occlusion of the lumina with thickening of the intima and thrombosis. Boyd³ and others, on the other hand, believe that syphilis is not an etiological factor in periarteritis nodosa. The

argument supporting this latter view is that syphilitic lesions are generally found in the elastic type of blood vessels, while periarteritis nodosa is a disease of the muscular type of artery. Though it is true that in several such cases reported in the literature there have been positive serological findings for syphilis, which led the authors to assume that the syphilitic virus was an etiologic factor in their cases, one should not overlook the fact that syphilitic patients may have periarteritis nodosa superimposed as a distinct disease process. Furthermore, even though the literature does not disclose the isolation of a single etiologic factor, aside from the little supported view of infection by unknown filterable viruses, periarteritis nodosa is definitely a clinical and pathological entity.

Clinically, the disease is rare and its diagnostic criteria are not sharply defined. No age is exempt and the occurrence is four to one in males. The clinical manifestations are so varied and bizarre that they may easily simulate a dozen or more diseases. A few of the commonest conditions with which it may be confused are trichiniasis, neuritis, miliary tuberculosis, gastro-enteritis, endocarditis, vascular nephritis and acute abdominal conditions. As to signs and symptoms, those of sepsis predominate, the commonest findings being fever, leukocytosis with or without eosinophilia, moderate to marked anemia, enlargement of the spleen, prostration and loss of weight. Localized manifestations depending on the locations of the main vascular lesions, are anginal attacks in coronary involvement, symptoms of "acute abdomen" in mesenteric vascular lesions, and polyneuritis in neuro-muscular lesions. It follows, therefore, that diagnosis is extremely difficult during life unless there are peripheral nodules, resection and microscopic examination of which give the diagnosis, or unless, as in the case reported by Bernstein,⁴ biopsy of skeletal muscle discloses the disease. Unfortunately, however, the majority of cases do not show peripheral nodules but, as in our case, only lesions which are confined to vessels of the viscera thus making pre-mortem diagnosis impossible. An autopsy study with careful microscopic examination of the blood vessels is then the only method of diagnosing the disease. In this connection Haming and Kimball⁵ pointed out that in this country we do not perform autopsies frequently enough, for in their excellent review of approximately 150 cases of periarteritis nodosa they found the majority recorded in foreign literature because of the greater number of routine autopsies carried out in clinics abroad.

Pathological findings and descriptions are fairly uniform in the majority of cases recorded. Gross lesions consist of small nodulations varying in size from that of a lentil to a split pea along the affected vessels. These nodules often involve the mesenteric vessels, but when the visceral vessels are the only ones involved, it is very easy to overlook gross changes by the naked eye. The lesions occur in the following organs and tissues in the order of their decreasing incidence: kidneys, heart, liver, gastrointestinal tract, pancreas, mesenteric arteries, muscles, and peripheral nerves. The central nervous system is least involved. Microscopically, various stages of inflammatory reaction and healing are seen in the walls of the small arteries and arterioles. In the early stage, the exudative process consists of polymorphonuclear infiltration of both the media and adventitia. Later, there are proliferative changes of the intima with subsequent thrombosis and occlusion of the lumen with or without dilatation above this site. In the late stages of the disease polymorphonuclear cells are few and

lymphocytes predominate and hyalin and fibrous tissue replace most of the layers of the vessels

SUMMARY

In a case of periarteritis nodosa, clinical observations, postmortem findings and a brief discussion of the subject are presented. The case is of further interest because, despite the mesenteric lesions and small infarctions of the bowel, no acute abdominal symptoms were present. Furthermore, the microscopic studies of the spinal cord did not explain the cause of pronounced neuritis of the extremities. Finally we would like to emphasize the value of routine postmortem examinations, especially in those cases of unknown sepsis, for without postmortem study certainly the diagnosis of this condition will be missed.

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A CASE PRESENTING PULMONARY AND OSSEOUS LESIONS PRESUMABLY DUE TO SARCOID

By HENRY F STOLL, M D, F A C P, [†] *Hartford, Connecticut*

EXCEPT among dermatologists, whose chief interest is confined to the skin manifestations, one rarely hears of sarcoid. The fact that there may be extensive involvement of the viscera and bones in addition to skin lesions appears to be quite generally unknown among internists though such cases were described over 20 years ago. When the skin manifestations are slight or even absent and the other lesions pronounced, a difficult diagnostic problem is presented as the case here reported illustrates.

CASE REPORT

W C, aged 14 years, was referred to me January 16, 1929, for examination because of cough. His general health had been good except that he suffered considerably from sinus disease. It had been observed that the cough was worse when he was having discharge from his sinuses. His appetite was excellent. He was quite free from symptoms other than the cough.

Examination. He was a frail lad with a flat, narrow chest. Height 65 inches, weight 105 lbs. Cervical glands showed slight enlargement. Pulse was 72 and temperature normal. The tonsils did not appear to be infected. With inspiration there was retraction of the lower third of the sternum and also of the epigastrium. There

* Presented at the Detroit meeting of the American College of Physicians, March 5, 1936.

[†] Deceased.

was a suggestion of increased whisper interscapularly but not enough to be significant. Roentgen-rays of the lungs (figure 1) by Dr Eliot S Cogswell showed some thickening at the roots and a certain amount of fine dappling throughout the lung fields. There were also some clusters of pin-head-size rather "soft" shadows.

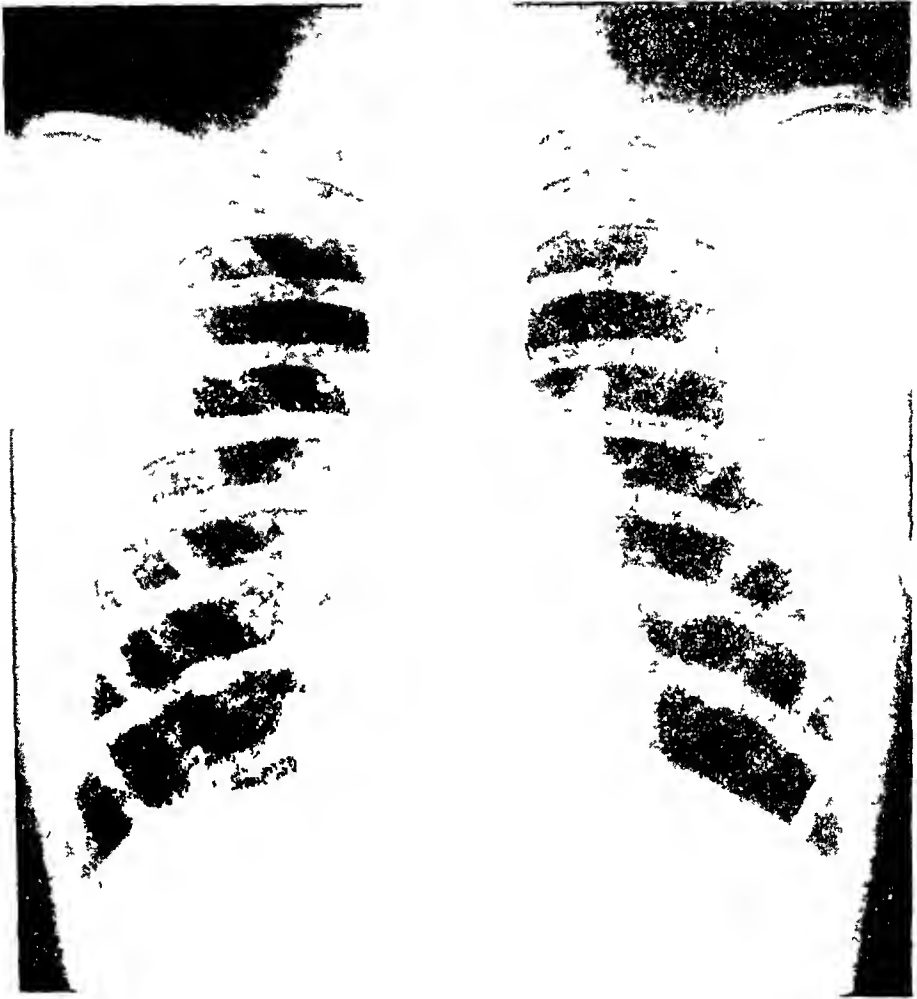


FIG 1 June 1929. A fine mottling is evident in the right midpulmonic field and one of less extent in the upper outer part of left lung. Physical signs were negative except for an indefinite D'Espine sign.

I was somewhat in doubt as to the significance of the roentgen-ray findings but felt that they were compatible with a chronic, non-tuberculous type of infection and probably were dependent upon his recurring attacks of sinus trouble.

After ascertaining that the patient was not running a fever, I felt that it was probably not a tuberculous process. I next saw him June 10, 1929 (five months later). He was very well, having been free from sinus trouble and gained 6 lbs in weight. He exhibited interscapular whisper to the fourth thoracic spine. December 27, 1929 (nearly a year after the first examination), he was very well. His weight was 120 lbs, a gain of 15 lbs since the first examination. There was still slight enlargement of the cervical glands, but no abnormal signs were noted in the chest. There was some mucopurulent discharge present on the postpharyngeal wall. A month later,

while out of the city he had an attack of pneumonia and is said to have been very ill. He made a good recovery and when seen six months later (June 1930) his weight was 126 lbs—an additional gain of 6 lbs in six months. He appeared then to be in excellent health except that five weeks previously the middle finger of the left hand had begun to swell and to be somewhat painful. At the time of my examination there was a definitely spindle-shaped swelling but the overlying skin was not involved. It did not appear to be particularly painful except on motion. A surprising amount of bone destruction was revealed by the roentgen-ray (Figure 4a).

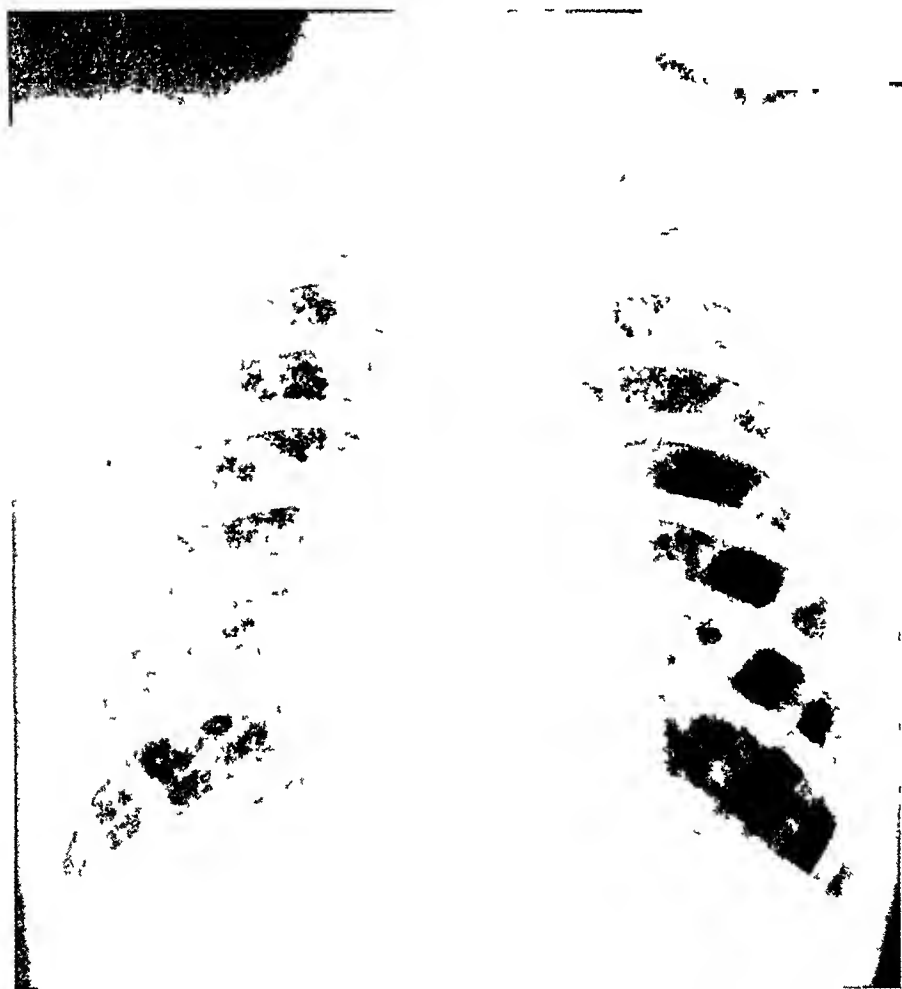


FIG 2 June 1930 Extensive "snowflake" infiltration of both lung fields somewhat more on the right, with moderate thickening of the hilar structures. Entire absence of physical signs except moderately positive D'Espine sign. General health appeared excellent. Normal temperature.

The roentgen-ray findings of the lungs at this time (figure 2) were even more astonishing. There was extensive, diffuse, soft mottling which was highly suggestive of miliary tuberculosis. From the films alone, one would be quite sure that the lesion was tuberculous, yet he was in excellent health, had gained in weight, was free from fever and with no physical signs of pulmonary disease. The destructive lesions of the bones of the hand were very suggestive of tuberculosis, yet the only pain he experienced was due to a fracture at the site of one of the lesions.

The lung findings were somewhat like the peribronchial, streptococcus pneumonia that occurred during the war, but it seemed unlikely that the lesion as revealed by the roentgen-ray would have persisted for six months. The indolent character of the lesion of the finger was unlike a streptococcus infection. A negative Wassermann appeared to exclude syphilis. I did not know what the pulmonary condition was, nor could I explain the destructive lesion in the bones. Tuberculosis was a strong possibility yet this diagnosis did not ring true.

A protection for the fractured finger was supplied and he was sent to a boys' camp where he was directed to engage in the usual camp activities except that he was to



FIG 3 June 1931 Lungs completely cleared. Hilar structures less dense. This film is even clearer than the one taken in June 1929 (figure 1) which suggests that the process, that was full-blown in June 1930 (figure 2), had really begun when the first film was taken. The attack of streptococcus pneumonia developed about mid-way between films one and two.

avoid all strenuous exercise such as athletic contests, etc. A rest period each afternoon was also prescribed. During the summer he gained 9½ lbs and was free from fever and cough. Roentgen-rays of the lungs at this time showed practically no change but the bony lesion (figure 4b) showed much improvement. There was no pain unless he grasped something very hard with the hand.

In June 1931, after spending the winter in Texas, he was in excellent shape. His

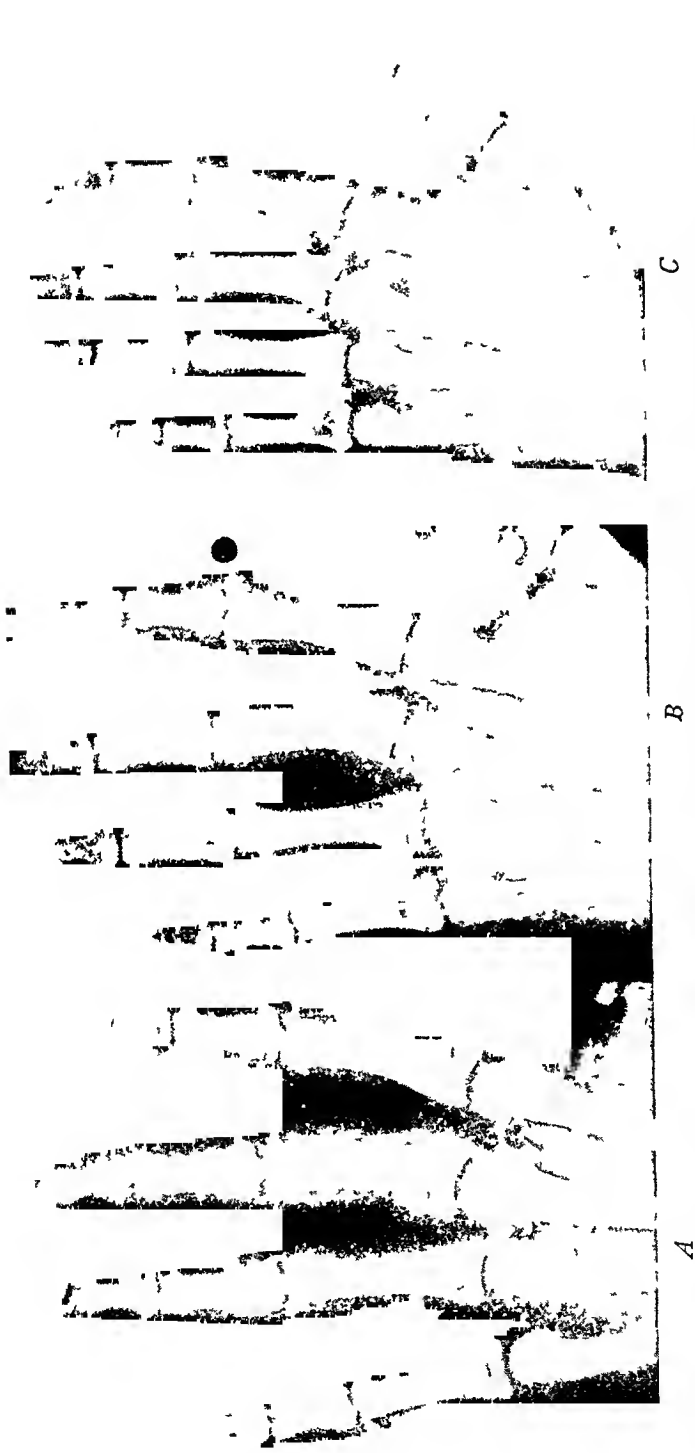


FIG 4 (a) Proximal end of the first phalanx of left middle finger shows a destructive lesion with fracture. The proximal end of the middle phalanx of the ring finger shows a similar but less marked lesion (b) Two months later definite improvement evident (c) One year after a Bone lesions have entirely subsided

weight at this time was 136 lbs 6 oz, a gain of over 31 lbs since the first examination 2½ years before. He was free from cough and the roentgen-ray of the lungs (figure 3) showed them to be entirely clear, better in fact, than at the time of my first examination. It seems probable that the findings noted in the first film, and absent in the last one, were due to the beginning of sarcoid which, by the time the next film (figure 2) was taken, had progressed. When last seen the bone lesions had entirely subsided (figure 4c).

By this time I felt sure that the condition was not tuberculosis though it was not until four years later, when Dr Francis T Hunter showed me the film of a similar case at Massachusetts General Hospital, that I realized that the condition was probably sarcoid. Dr Hunter has since published his case, and the controversial points as to the priority of its recognition and the different views as to the etiology are dealt with in his presentation.

DISCUSSION

Sir Jonathan Hutchinson appears to have been the first to describe one of the skin manifestations of this interesting disease nearly a quarter of a century before Boeck's article appeared. The latter gave a detailed report of the histology and suggested the name "Sarcoid" (sarcoma-like) because of the infiltrative tendency somewhat suggesting the lymphoblastoma group.

Considered first a disease of the skin, it was not until 1902 that Kienbock² reported what he designated as "bone cysts" in a case of sarcoid. In 1915, Kugnitsky and Bittorf³ described visceral lesions showing the same histologic picture in the lungs, bronchial glands and other viscera. By some the condition is considered a manifestation of tuberculosis. Those championing this etiology explain the almost universally negative tuberculin reaction and the failure to find tubercle bacilli in the lesions, to what they term a condition of "anergy"—a relative or complete stage of desensitization. Goeckelman⁴ and Sulzberger⁵ among others, present arguments in support of a tuberculous etiology. The subject of sarcoid was discussed at length by the European dermatologists in 1934. Jens Nielsen,⁶ chief of clinic of the Finsen Institute, Copenhagen, considers it a definite clinical entity. He observed that there was pulmonary involvement (including bronchial glands) in 37 of 46 cases with skin manifestations. In none of them were there clinical or stethoscopic signs of pulmonary involvement.

The condition is benign, torpid and very chronic. Nielsen mentions the possibility of complete resolution but states that the pulmonary lesions are more apt to be stationary. For this reason the case here reported is unique in the rapidity with which the lung cleared. Piérard⁷ says that the pulmonary lesions are characterized by proliferation, they are not exudative in type and there is no tendency to break down and form cavities. Nor do they show a tendency to heal with the production of calcium. There is a lack of peribronchial pattern of lesions, and absence of calcification and of cavity formation. The roentgenogram may resemble miliary tuberculosis, or miliary carcinomatosis, or periarteritis nodosa. In all of these, however, the patient is acutely ill. It is also said to resemble the "sand-paper" mottling of leprosy. Typical sarcoid tissue has been found in the lungs at autopsy. The "bone cysts" (*osteitis multiplex cystica*) are fairly frequent and most common in the bones of the hands and feet. In the case here reported they healed with surprising rapidity as the roentgen-rays show. Kissmeyer,⁸ likewise, considers the disease a specific, chronic granulomatous process, standing midway between tuberculosis and leprosy.

No skin lesion was noted in the patient here described. This should not be interpreted as excluding a small inconspicuous lesion that might easily have been overlooked or thought to be of no consequence. However, members of his family do not recall any skin lesions. Increasing knowledge of the disease may demonstrate that skin lesions are not always present.

Various drugs have been tried with results that are not convincing. In this case, under a regime of outdoor life, with moderate exercise, a great deal of rest and a well-balanced and abundant diet, the recovery was prompt and complete, both the osseous and pulmonary lesions completely resolving.

SUMMARY

A case believed to be sarcoid of the lungs and bones is presented in which skin lesions were absent or minimal. Complete recovery, as demonstrated by roentgenological study, took place with surprising promptness under a regime of somewhat restricted exercise, ample rest and a generous, well-balanced diet.

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EDITORIAL

SNAKE VENOM IN HEMORRHAGIC STATES

THE value of moccasin venom in the control of hemorrhage was pointed out by Peck and Rosenthal¹. Peck had earlier found that moccasin venom would produce a refractory state to experimental purpura, or the Schwartzman phenomenon. For a number of years venom of various snakes has been suggested for innumerable diseases, but more definitely in relation to the production of hemostasis by direct application to the bleeding area. It was not until the work of Peck and Rosenthal with the parenteral use of moccasin venom that definite improvement was obtained in certain so-called secondary hemorrhagic states. The exact action of the venom is not known, but it has been assumed that the action is due to a change in the capillary walls resulting in a lessening of their permeability and thus preventing extravasation of blood. Moccasin venom was chosen because it seemed to produce the best results, although some improvement has been obtained with the venom of the copperhead. Cobia venom, since it is largely neurotoxic, has been used with fairly satisfactory results in cases of intractable pain.

Peck and Rosenthal in 1935 reported a series of cases of secondary and primary blood dyscrasias, with particularly good results in that group of diseases associated with some abnormality of the vascular wall. The dose recommended and used most generally is, for patients ten years old or older, an initial subcutaneous injection of 0.4 cc., with a rapid increase in the dose on subsequent injections to 1.0 cc. as a maximal. The reaction of sensitivity, which occurs in most patients on the third or fourth injection, is characterized by a local area of heat, redness, and swelling without much evidence of systemic reaction. At this time desensitization should be carried out by reducing the dose to a minimal quantity, approximately 0.05 cc. This is maintained until all evidence of reaction disappears, at which time the dose may be gradually increased to the full amount of 1.0 cc. twice a week. After hemorrhage has been controlled, the interval between injections may be lengthened to a week or longer depending upon the severity of the original hemorrhagic condition.

Moccasin venom has proved to be of definite value in the treatment of idiopathic epistaxis, bronchiectasis with hemoptysis, and functional menorrhagia, and fairly satisfactory in the treatment of toxic or secondary purpura.

¹ PECK, S. M., and ROSENTHAL, N. Effect of moccasin snake venom (*Ancistrodon piscivorus*) in hemorrhagic conditions, *Jr Am Med Assoc*, 1935, civ, 1066-1070.

PECK, S. M., CRIMMINS, M. L. and ERF, L. A. Coagulating power of *Bothrops atrox* venom on hemophilic blood, *Proc Soc Exper Biol and Med*, 1935, xxxii, 1525-1527.

PECK, S. M., ROSENTHAL, N., and ERF, L. A. The value of the prognostic venom reaction in thrombocytopenic purpura, *Jr Am Med Assoc*, 1936, cvl, 1783-1791.

puric states Peck and Rosenthal also had fairly good results in cases of hereditary multiple telangiectasis, they reported four cases, in two of which very definite improvement was obtained They emphasized the fact that in this particular condition it is important to continue the use of venom over a long period of time In diseases associated with changes in the blood, such as thrombocytopenic purpura, fairly good results were obtained and a definite response was noted in the majority of cases in their group In certain instances improvement was obtained without affecting any change in the blood itself, which would seem to bear out the contention that the action of venom is primarily upon the blood vessels On the other hand, cases of hemophilia, aplastic anemia, and leukemia show little response to venom therapy

In 1936 Watkins and Mussey² confirmed the findings of Peck and Rosenthal in cases of functional menorrhagia, and in 1937 Watkins and Thompson reported a series of twelve cases of essential hematuria, in eleven of which there was cessation of hemorrhage

It would seem, at least at present, from the work that has been done that moccasin venom is of definite value in the control of certain types of hemorrhagic conditions However, the experience with the venom has as yet been too limited to state what the ultimate results will be In some instances recurrences have been noted which may be controlled by resumption of the use of venom, in other instances there seems to be complete cessation of all hemorrhage Until the material has been in use over a longer period of time, and its use confined to secondary hemorrhagic states, it will be difficult to determine its real efficacy in the permanent control of hemorrhage

C H W

² MUSSEY, R D Discussion, Proc Staff Meet Mayo Clinic 1936, 31, 263-264

WATKINS, C H Experience with snake venom in menorrhagia, Proc Staff Meet Mayo Clinic, 1936 31 261-263

WATKINS, C H, and THOMPSON, G J Results in treatment of essential hematuria with moccasin venom, Proc Staff Meet Mayo Clinic (In press)

REVIEWS

Applied Dietetics for Adults and Children in Health and Disease By SANFORD BLUM, M D 408 pages, 24 × 16.5 cm F A Davis Company, Philadelphia 1936 Price, \$4.75

This book has many shortcomings. Published as a new book, it is essentially a revised and enlarged edition of "Practical Dietetics for Adults and Children in Health and Disease" published as a second revised edition in 1926. The present volume follows practically the same formula as its forbear of 10 years ago. It is divided into two parts, the first of which is entitled "Dietary for Adults in Health and Disease", the second, "Dietary for Infants and Children in Health and Disease". Diets are arranged alphabetically according to the title of the healthy or disease state. In comparing the 1926 and 1936 editions there is little to show that advances have been made in the field of dietetics.

To be sure there are new sections as, for example, those on pernicious anemia, carcinoma of stomach, diverticulitis, gall-bladder infection, gonorrhea, hemorrhage from stomach, indigestible foods and combinations, inorganic elements essential to nutrition, pneumonia, salt-free diet, and salt-poor diet. There is also some elaboration of the sections devoted to colitis and diabetes including a discussion of diet with insulin therapy. Occasionally a good deal of common sense is condensed into short chapters such as those devoted to "Dietetics Fads and Fallacies" and to "Vitamins". Incidentally there are practically no changes in Part II of the volume in the 10 year period from 1926 to 1936.

It is difficult to discuss the specific diets offered in this book without being too critical. Perhaps it will suffice to say that many of the diets are far too inadequate and cannot possibly accomplish the end result for which they are prescribed. Very often the choice of foods is without scientific basis. Furthermore it is doubtful whether a person's occupation, be it business or society, woman or college professor, really plays a *predominant* role in the selection of a specific diet. Such notations are dramatic rather than instructive.

In brief, then, this book has not kept abreast of advances in medicine. It represents one of that group of compendiums which in trying to be of service to the busy practitioner often mislead him in his selection of diets as well as in his knowledge of the essentials upon which careful dieting is based.

S M

Dietetics for the Clinician By MILTON ARLANDEN BRIDGES, M D, B S, F A C P Third Edition 1055 pages, 24 × 15 cm Lea and Febiger, Philadelphia 1937 Price, \$10.00

Although the general plan of this third edition has not been changed the book has grown in size from 666 to 970 to 1055 pages through its three editions. According to the author the present volume represents "a relatively new text-book based upon more accurate and up-to-date foundations."

Examination discloses a remarkable and comprehensive treatise. All of the good features of the two previous editions have been retained and in addition the subject matter has been augmented and rewritten so that it becomes one of the most useful reference books in the field of dietetics. The sections prepared by specialists are a feature of the book. Some overlapping and repetition result but these have been reduced to a minimum.

The material pertaining to the mechanics, physiology and chemistry of digestion has been markedly condensed and shorn of extraneous, non-practical discussion. For

convenience, the various disease entities are arranged alphabetically and presented according to the following general plan. Each disease is first the subject of a brief general discussion after which there follows a detailed listing of those foods to be omitted, as well as those allowed in limited quantities. Finally, there is a presentation to the reader, and hence to the patient, of a series of practical edible items of food, readily obtainable, arranged in accordance with the previously outlined principles. Wherever indicated there are added a number of practical medical and culinary suggestions.

The author recognizes that dietotherapy is often empirical and that there are diverse opinions regarding the dietary management of many diseases. Previous editions have been criticized for inconsistencies between the diet and the pathological physiology underlying the diseases under discussion. Such criticisms may, however, be omitted, especially since it is apparent that a sincere attempt has been made to include only those diseases in which, in the opinion of the author and his contributors, diet plays a rôle. With some exceptions they have admirably avoided contentious matter.

The food tables are very comprehensive and well arranged. Under "Distribution of Foods" are included lists showing those foods highest or lowest in Ca, I, Fe, Vitamins A, B, etc., there are also lists showing flatulence-producing foods, fluid foods, soft foods, neutral ash, acid and alkaline-ash foods, etc. It is a comfort to know that data of this kind can be found in one book. Traditional and dietetic evaluation of foods are compared. In the appendix, written in collaboration with Majorie R. Mattice, are listed numerous other tables replete with information concerning food analyses and showing their nutritive, mineral and vitamin values.

The book will be well received because it supplies with authoritative clarity, and in a practical and detailed manner, valuable information in the field of dietetic treatment.

S M

Theory and Practice of Psychiatry By WILLIAM S. SADLER, M.D. 1231 pages, 26 × 18.5 cm. C. V. Mosby Company, St. Louis, Missouri. 1936. Price, \$10.00.

This book was written as a "psychiatric textbook for neuropsychiatric specialists and general practitioners of medicine" and "a reference handbook for psychologists, sociologists, pastors and other professional readers." It consists of 1155 large pages, 2 pages of excellent bibliography, containing almost entirely books rather than articles, 34 pages of glossary and a complete index. It is divided into a good historical introduction which, among other things, outlines the various schools of thought, and five sections.

The first, headed *Theory of Psychiatry*, 233 pages long, is a resume of psychology and psychopathology. It contains a great many definitions, a good deal of illustrative material. Part II, *Personality Problems*, devotes 191 pages to a discussion of personality, classifications of personality, the question of integration, and personality problems at various age levels. Part III, *The Neuroses*, contains an exhaustive presentation of the author's concept of the origin, characteristics, motivations, symptomatology and treatment of these borderline states. Part IV, in 121 pages covers the *Psychoses*, that is the major mental illnesses. The rest of the book, Part V, deals entirely with *Psychotherapeutics*.

The book concerns itself primarily with the study and treatment of non-institutional patients of the sort that may be expected to present themselves to general practitioners. It is exceedingly readable. This is a distinct tribute to a volume of this size. One's interest does not lag at any point, however much one may disagree with the author. Early in his writing he tells us that he personally agrees in most respects

with orthodox views, but he here sets forth utilitarian concepts he finds clinically useful. He is certainly resourceful, never loses sight of the broader aspects of the problem with which he has to deal, and does not hesitate to make use of any means to help restore his patient to health.

We conceive it to be the duty of a reviewer in a special field to give individuals outside his particular branch of medicine his reactions to a book which entirely concerns itself with that special field. We have read most of this large volume twice and have been unable to escape the feeling that this might have been an enduring classic if it had been condensed into 250 or 300 pages. There is much throughout the book which is exceedingly worthwhile. It is a volume which should be read in its entirety or not at all. Otherwise, it is likely to give rise to distinct misunderstandings. An example is the statement on page 477, in which we are told to "laugh heartily at his fears and get him (the patient) to join in the laughter. Ridicule is the master cure for fear." Dr. Sadler is too good a psychiatrist and too kindly a man to imply that we should ridicule the patient himself. In many places he explicitly warns us against doing so. This is typical of many instances throughout the book.

There are many repetitions, there are too complex classifications of personalities—almost as many as there are individual case histories presented. There is very little effort to group them. One gets the impression of hair-splitting minor variations. The chapter on Classifications of Personality, for example, contains a Psychosociologic Classification into 12 groups under such headings as Deficient Personality, Perverted Personalities, Criminal Personalities, etc., an Intellectual Classification of Personalities, a Sociologic Classification of Personalities, Temperamental Types of Personality, Endocrine Classification of Temperaments, including such statements as

"The Gonad-Dominant Type—This type is generally found to be secretive, sly and receptive. They are not always outwardly sensual appearing, but thorough acquaintance reveals that their entire lives are motivated by the sex urge", a Sensory-motor Classification, a paragraph on Behaviorism and a short section entitled, Other Classifications. We feel that any such discussion as this would be very likely to hopelessly befuddle most individuals and might prove exceedingly misleading to some of the groups, such as pastors and sociologists, for whom the book is written. There are too many vague descriptions of personality distortions or of neurotic pictures. Throughout the book he speaks of such things as Master motives, Master psychobiologic drives, the psychology of self-deception, discussions of self-realization, moral maladjustment, cosmic maladjustment and realizing personality potentials which seem to us to have little place in a psychiatric textbook, tinged as they are by more than a trace of semi-religious exhortation similar to the type found in so many of the "Know Thyself," "Quest for Happiness" popular psychologies which have flooded the book-stalls in the past few years.

The section on Psychotherapeutics contains a great many exceedingly helpful suggestions and technics. Chapters 68, 69, 72 and 73 are good. There is a timely and worthwhile chapter on the teaching of psychiatry and psychiatrists. Chapter 74, listing and explaining various philosophies of life, is interesting, but the whole 230 pages of this section are so interlarded with what amounts to "pep talks," slogans such as "Hold the fort," "Sand the track," "Play the game square and take the score like a man" as to create a great deal of difficulty in separating the wheat from the sort of chaff best illustrated by his instruction as to the technic of mastering fear, which (page 974) consists in getting the patient to assume the following attitude: 1 Do not fear it, 2 Do not fight it, 3 Do not disown it, 4 Do not try to run away from it, 5 Utilize fear as a fight stimulus, 6 Refuse to foster fear curiosity, 7 Unmask fear, 8 Avoid the fear habit. The tendency to moralize and to make appeals to one's better self are constantly present as in "Conscious conflict, when viewed squarely and faced bravely, is the battle cry of one's better self, calling for the mobilization of all

the powers of the idealism of the personality for the purpose of effecting the psychic conquest and subsequent ethical and moral elevation of one's natural emotional impulses and innate biologic urges" We respectfully submit the point of view that few of us are innately equipped to exhort our patients with sufficient conviction to even send them away from our offices with a temporary glow of well-being, let alone effect lasting benefit

H M M

Tissue Immunity By R L KAHN, M S, D Sc 707 pages, 23.5 × 17 cm Charles C Thomas, Baltimore, Maryland 1936 Price, \$7.50

This book presents a thorough exposition of the author's ideas on the rôle the tissues in general play in resistance to infection There is no attempt to substitute one theory of immunity for another, but merely to extend and enlarge the concept of the immunological responses to bacteria and other antigens These responses are considered a physiological function of all cells and are believed to have their evolutionary origin in parasitism Tissue immunity is not only philosophically discussed but many experiments are described in substantiation of the author's views These demonstrate the reaction to an antigen of various tissues in the non-immune state, in the naturally immune animal, at different stages in the rise and fall of acquired immunity, and finally in the condition of "disimmunity" The clinical significance of these responses is given full consideration Though it is not impossible that exception will be taken to some of the conclusions drawn from the experiments, this book is undoubtedly an important and stimulating contribution to the literature on immunology and one that may be unhesitatingly recommended both to the clinician and to the specialist in this field It is, however, regrettable that the style of presentation is not more pleasing

F W H

Heart Disease and Tuberculosis By S ADOLPHUS KNOPP, M D 108 pages, 20.5 × 14 cm The Livingston Press, Livingston, New York 1936 Price, \$1.25

The author has played an active part for many years in anti-tuberculosis work In this small book he gathers together in brief form many rather disconnected observations upon the present status of preventive methods in both diseases The importance of diaphragmatic breathing as a preventive and even a curative method is heavily stressed

M C P

Modern Urology By HUGH CABOT, M D 1813 pages, 24.5 × 17 cm Lea and Febiger, Philadelphia 1936 Price, \$20.00

Cabot's *Modern Urology* is well named for it brings up to date every phase of urology and does it very efficiently The chapters are written by different authors who are authoritative and who well represent urology in America The book is in two volumes, is well edited, and is profusely illustrated The first volume is divided into six sections dealing with the lower urinary tract It contains a chapter dealing with methods of diagnosis which is unusually informative and a chapter on transurethral resection of the prostate gland, which, while enthusiastically written, is nevertheless a well balanced description of the procedure and its results in the hands of the urologists in this country most proficient in its use The open types of operation on the prostate gland are also very well described by able and experienced surgeons

The second volume is divided into four sections, dealing with conditions in the bladder, ureters and kidneys. The chapters on stone present the newer conceptions of stone formation. The article on anomalies of the kidneys and uréters is probably the best and most complete information on this subject that has appeared in years. Tumors of the kidney have been particularly well presented, and the classification of these tumors which is offered is based on sound reasoning. The last section deals with radiation therapy of tumors of the genito-urinary tract. This section discusses the radiosensitivity of cancers and classifies tumors accordingly, and indicates the manner in which these various tumors are to be radiated and the results in a large experience. It is a very valuable section.

Cabot's *Modern Urology* is a book that every urologist should possess. It should also be accessible to general surgeons, general practitioners and students as the best encyclopedia of urology.

COLLEGE NEWS NOTES

THE NEW HEADQUARTERS OF THE AMERICAN COLLEGE OF PHYSICIANS

In accordance with action initiated by the Board of Regents and the Board of Governors of the College at the 1936 Annual Session, the College acquired by purchase the former residence of Charles J Eisenlohr at 4200 Pine Street, Philadelphia. The permanent headquarters building is illustrated herewith. The building occupies a plot of ground approximately two hundred feet square, bounded by South Forty-Second Street on the east and by Pine Street on the north. The grounds are beautifully landscaped, with many attractive shrubs, evergreen and deciduous trees. The

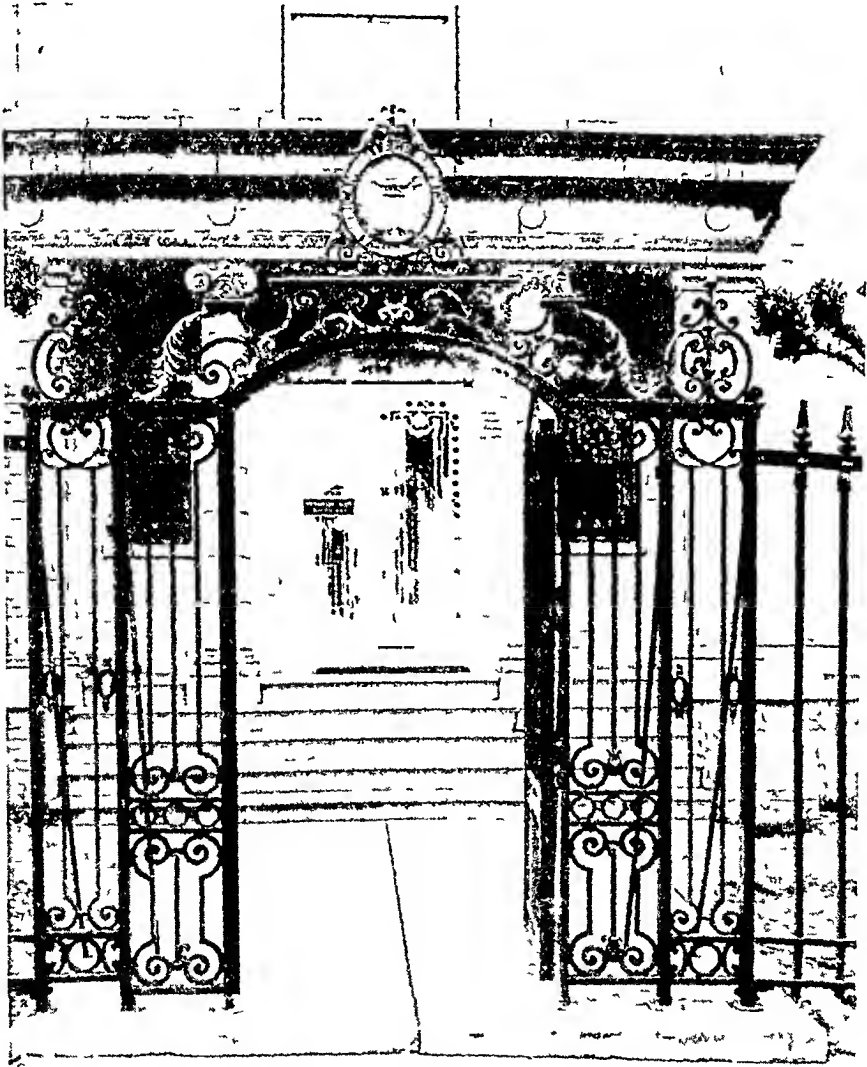


FIG 1 Main entrance



FIG 2 View of the garden and building from the south

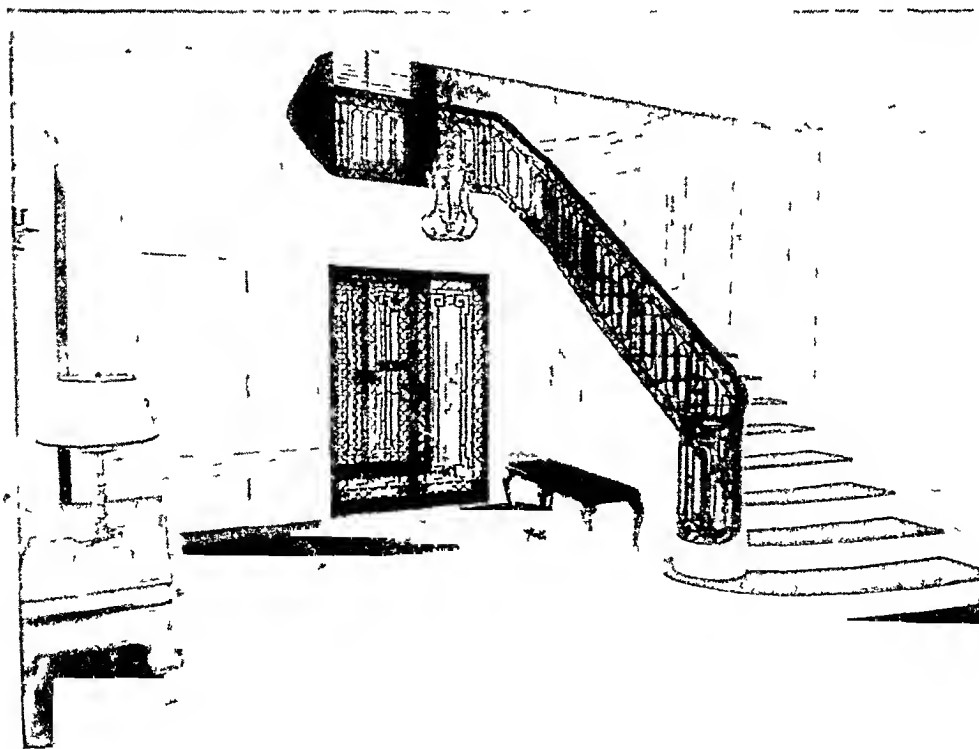


FIG 3 Reception hall and staircase

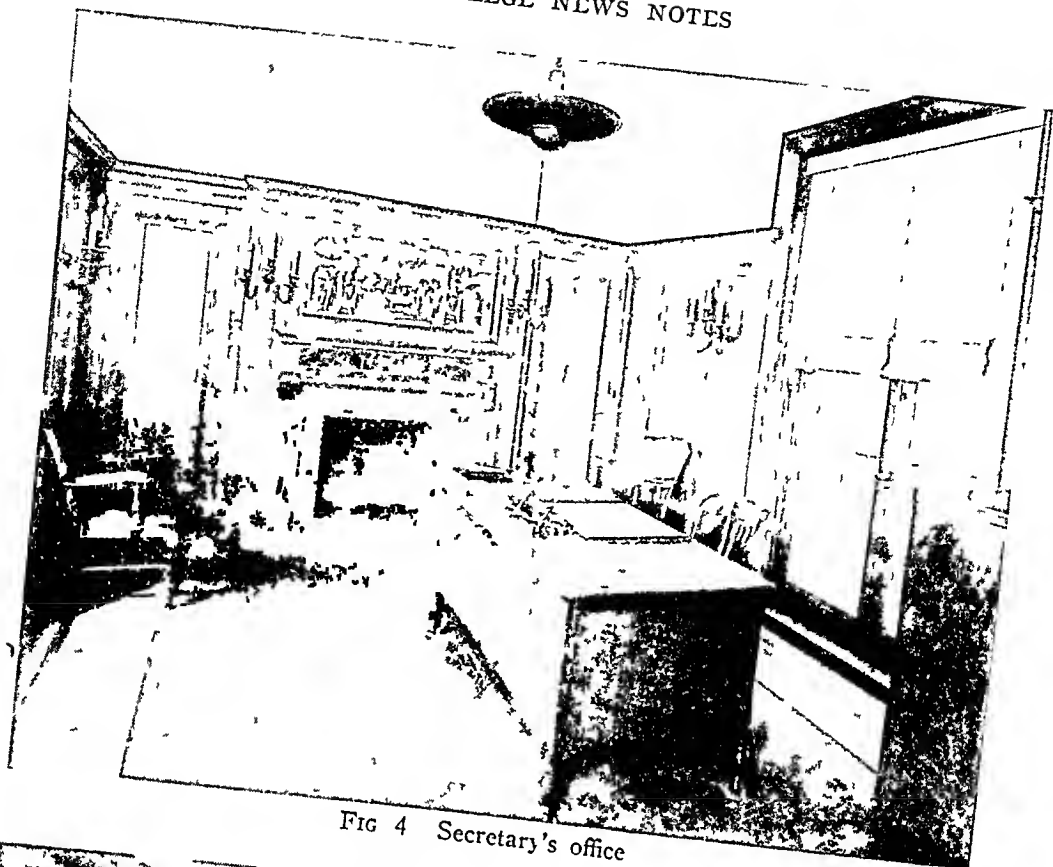


FIG 4 Secretary's office



FIG 5 Executive Secretary's office

house was built in 1906-07 from the architectural plans of Horace Trumbauer, who has attained an enviable position as an architect from the many beautiful and practical buildings he has designed, among them being the new Duke University at Durham, N C The following architectural details of the College's new home may be of interest to the members

"In style it is based on the tradition of the late Eighteenth Century French Architecture of the period of Louis XVI In composition it consists of a main mass and a lower wing The main part is sub-divided into a central portion with a pavilion on each end, accented on the first floor with tall windows surmounted by pediments supported on consoles The main walls are two stories in height and are



FIG 6 Lounge and Board room

crowned with rich cornice and high mansard roof, this latter being metal crested and terminating in moulded finials

"The main body of the walls is constructed of gray buff brick accented by the terra cotta cornice, window, and entrance and porch details

"The property is surrounded by a wrought iron fence designed in the same general style as the house and is recalled in the house by the wrought iron doors and window grilles at the main entrance and doors to the south porch

"The decorative treatment of the interior is consistent with the style of the exterior and again follows the Louis XVI style The rooms are paneled in wood with decorative plaster cornices and marble mantels"

The location is but a few squares removed from the University of Pennsylvania and the Philadelphia College of Pharmacy and Science Excellent transportation facilities are available through surface and subway-surface trolley lines, furthermore, it is within convenient distance of the new West Philadelphia Station (Thirtieth

Street) of the Pennsylvania Railroad and the Twenty-Fourth Street Station of the Baltimore and Ohio Railroad

The house answers the long pressing need for adequate offices, committee rooms and a Board room for the College. With a minimum of alteration, the house has been admirably arranged for the work of the College. Spaces are available for the College Library of publications by members, for various meeting rooms and for social gatherings of members. On the second floor are available rooms in which examinations of the American Board of Internal Medicine may be held when these examinations are scheduled for the Philadelphia territory, also rooms where members may conduct private conferences when in Philadelphia.

The members of the College are cordially invited to visit and inspect the new College building and to use it for their headquarters when passing through Philadelphia.

THE COLLEGE LIBRARY OF PUBLICATIONS BY MEMBERS

Considerable progress has been made in establishing a College Library of books of which our members are the authors. This Library, in a sense, is a memorial library to our members. A general medical library, other than one composed of publications by the members, is scarcely justified, because there are so many other general medical libraries available in Philadelphia.

A little booklet indexing all the books that have been donated to the College Library will be ready for distribution at the College Booth at the St. Louis Session, April 19 to 23.

We gratefully acknowledge the following recent contributions:

Books

- Dr. Ray M. Balyeat (Fellow), Oklahoma City, Okla., one autographed book, "Allergic Diseases: Their Diagnosis and Treatment",
- Dr. Charles A. Doan (Fellow), Columbus, Ohio, one autographed book, "Clinical Implications of Modern Physiologic Hematology",
- Dr. Harry A. Pattison (Fellow), Livingston, N. Y., one autographed book, "Edward Livingston Trudeau, A Symposium" (with Lawlason Brown, Allen K. Krause and Charles G. Trembley),
- Dr. Willard J. Stone (Fellow), Pasadena, Calif., one book, "Bright's Disease and Arterial Hypertension".

Reprints

- Dr. M. Coleman Harris (Fellow), New York, N. Y.—1 reprint,
- Dr. Samuel E. Munson (Fellow), Springfield, Ill.—1 reprint,
- Dr. Robert Sterling Palmer (Fellow), Boston, Mass.—3 reprints,
- Dr. John W. Shuman (Fellow), Los Angeles, Calif.—1 reprint,
- Dr. Edward L. Turner (Fellow), Nashville, Tenn.—12 reprints,
- Dr. Hyman I. Spector (Associate), St. Louis, Mo.—4 reprints,
- Dr. Hugh Stalker (Associate), Grosse Pointe, Mich.—1 reprint.

Dr. Elliott P. Joslin (Fellow), Clinical Professor of Medicine, Harvard University Medical School, Boston, delivered the ninth annual Ranson Lecture at Northwestern University, February 3, on protamine insulin.

Dr Samuel M Bittinger (Fellow), assistant superintendent of the North Carolina Sanatorium, Sanatorium, N C, will be the director of the Western North Carolina Sanatorium now under construction, near Asheville Dr Paul P McCain (Fellow), superintendent and medical director of the North Carolina Sanatorium for the Treatment of Tuberculosis, will have general supervision over the new institution

Dr Roscoe L Sensenich (Fellow), South Bend, Ind, has been elected president of the Northwest Medical Conference

Dr Thomas Parran (Fellow), Surgeon General of the U S Public Health Service, delivered the Gehrman Lectures at the University of Illinois College of Medicine during March on the subjects "Health as a Factor in Social Security," "Industrial Hygiene" and "Syphilis"

Dr Alfred R Masten (Associate), Denver, has been appointed director of a newly created division of tuberculosis control under the Colorado State Board of Health

Under the auspices of the Fulton County (Ga) Medical Society, Dr Henry W F Woltman (Fellow), Professor of Neurology, University of Minnesota Graduate School of Medicine, delivered the E Bates Block Memorial Lecture in Atlanta, January 28, on the subject, "Postoperative Neurologic Complications"

The fifth annual graduate clinic of the George Washington University School of Medicine, Washington, D C, was conducted during February, with the following Fellows contributing

Dr William E Clark, "Duodenal Ulcer",

Dr Walter A Bloedorn, "Relation of Clinician and Pathologist",

Dr Roger M Choisser, "Sudden Death A Clinical Pathologic Consideration with Case Presentations"

Dr Henry J John (Fellow), Cleveland, Ohio, was the recipient of the Eisenman Award of the Cleveland Jewish Welfare Federation at a meeting on February 4, the award being made in recognition of his work for diabetic children in Cleveland

Dr Edward B Krumbhaar (Fellow), Philadelphia, Pa, has been elected vice president of the College of Physicians of Philadelphia



DR WILLIAM ALLANSON WHITE

OBITUARIES

WILLIAM ALLANSON WHITE

William Allanson White (Fellow), an eminent physician, a pioneer psychiatrist of international renown and a gallant gentleman, died on March 7, 1937, in his apartment at St Elizabeths' Hospital of which he had been Superintendent for the past thirty-four years

Dr White was born in Brooklyn, New York, on January 24, 1870, graduated from Cornell University in 1889, and from Long Island Medical College in 1891. In the following year he was appointed second Assistant Superintendent of the New York State Hospital for the Insane at Binghamton

In 1903 President Theodore Roosevelt appointed Dr White Superintendent at St Elizabeths, then known as the Government Hospital for the Insane at Washington, D C, a position which he held at the time of his death. He was Professor of Psychiatry at George Washington University, the U S Army Medical School, the U S Navy Medical School, and until 1932 at Georgetown University School of Medicine, a position which he relinquished because of pressure of work. He was a Fellow of the American College of Physicians, a member of the National Research Council, a member of the Board of Directors of the National Committee for Mental Hygiene, Ex-President International Committee for Mental Hygiene, Councilor, Medical Council, U S Veterans Administration, member and former Secretary Federal Board of Hospitalization, Ex-President American Psychiatric Association, American Psychopathological Society, American Psychoanalytic Society, Psychoanalytic Society of the District of Columbia, The Society of Nervous and Mental Diseases, Washington, D C, Medical Society of the District of Columbia, American Medical Association, American Institute of Criminal Law and Criminology, American Neurological Association, American Anthropological Association, Tri-State Medical Association, Washington, D C Psychopathological Association, New York Psychiatric Association and many other learned Societies and Associations

Dr White was a prolific writer, his articles appearing in the leading medical and scientific journals of this and many foreign countries. He was the author of the following books

"Insanity and the Criminal Law" (Macmillan)

"The Meaning of Disease" (Williams and Wilkins)

"Mechanisms of Character Formation" (Macmillan)

"Principles of Mental Hygiene" (Macmillan)

"Mental Hygiene of Childhood" (Little, Brown & Co)

Textbook on Nervous and Mental Disease—with Jelliffe (Lea and Febiger)

- "Outlines of Psychiatry"—14th Edition (Nervous and Mental Disease Publishing Company)
- "Mental Mechanisms" (Nervous and Mental Disease Publishing Company)
- "Introduction to the Study of the Mind" (Nervous and Mental Disease Publishing Company)
- "Essays in Psychopathology" (Nervous and Mental Disease Publishing Company)
- "Lectures in Psychiatry" (Nervous and Mental Disease Publishing Company)
- "Thoughts of a Psychiatrist on the War and After" (Paul B Hoeber)
- "Twentieth Century Psychiatry" (W W Norton & Co)
- "Modern Treatment of Nervous and Mental Disease" With Dr Smith Ely Jelliffe (Lea and Febiger)
- "Crimes and Criminals" (Farrar and Rinehart)
- "Foundations of Psychiatry" (Nervous and Mental Disease Publishing Company)
- "Forty Years of Psychiatry" (Nervous and Mental Disease Publishing Company)
- "Medical Psychology" (Nervous and Mental Disease Publishing Company)

It is difficult now and will be increasingly so in the years to come for the medical men of the National Capitol who had come to rely upon Dr White's wise counsels in trying situations affecting public policy, as well as in matters medical, to realize that he has gone forever from among us

His wide and constant contacts with men in public life and his long experience in matters before Congress enabled him to render valuable service to local medical organizations as well as to many other such organizations throughout the land. Bills in Congress affecting the healing art were constantly submitted to Dr White for his opinion, and many were the hidden pitfalls which his keen analytical mind discovered. No day was too crowded for him to pause and respond to the call for aid from a brother practitioner. His friends often marvelled that he could afford the time to attend conferences on civic as well as professional matters. As Superintendent of St Elizabeths Hospital he was responsible for the well being of approximately six thousand patients and a thousand employees, in addition to the direction of his professional staff. Dr White would have had little interest in an Institution devoted largely to merely custodial care of the mentally afflicted. The goal set by St Elizabeths during his Superintendency was curative treatment.

While a student at Cornell he resolved, as Herbert Spencer has asserted, that it is possible for an intelligent man to acquire a comprehensive knowledge of every subject. He recognized the tremendous personal effort that

would be involved in even approximating the accomplishment of this ideal. In setting himself to the task, he determined that while mental medicine should command his prime attention, a wide acquaintance and familiarity with other sciences and with organized effort for political and social advancement would enable him to better serve the cause of his chosen profession.

Thus we find him a voracious reader, not getting books from libraries but purchasing them so that they would always be at hand for ready reference. Astronomy, anthropology, medieval and modern art and architecture, engineering, the principles of the law, sociology, political economy, these are some of the subjects which were read with avidity, and absorbed by his wonderful intellect. Soon it was apparent that important works in foreign tongues must be read in the original. To acquire this facility he enrolled in a foreign language school, mastering German and acquiring a working familiarity with French, Spanish and Italian.

All the while he was devoting himself assiduously to his profession. Recognizing that European Universities and laboratories were forging ahead in the diagnosis and treatment of various forms of mental disorder, he spent several summers as a student at the feet of the masters and in laboratory research. On each return he would apply to the great work at St. Elizabeths important results of his foreign studies and observations.

It was becoming apparent that his understanding of the mental processes of others was made clearer by reason of his general knowledge of other subjects. He must keep abreast of all things touching human life that he might definitely accomplish something for the mentally afflicted.

The field needed many more workers, men and women who would devote themselves intelligently and whole-heartedly to the high purpose for which he was giving his life. These must be thoroughly trained physicians, capable of working with him in the field of mental medicine. Already, with Jelliffe he had written the *Outlines of Psychiatry*, destined to be a standard textbook in all medical schools of the country. To supplement this and to urge young physicians to enlist in the cause he lectured to students in Washington and New York, wrote an astounding number of books and articles for professional journals, talked before important gatherings throughout the land, and personally developed at St. Elizabeths several score of men and women who attained superintendencies and ranking positions in other hospitals.

Men marveled that he could accomplish so much. The extent of his professional activities seemed boundless. A happy orderliness in all affairs was of material aid in the effectuation of his plans and ambitions. Required by law to live at St. Elizabeths, he made it a practice whenever possible to spend three or four evenings away from the Institution. During these periods he was outside the atmosphere of the abnormal, was circulating among normals, enjoying a change of surroundings, refreshing his mind often at the theatre of which he was a devotee. When so refreshed, he

was ready for more work, and probably the great majority of his books were written between midnight and three in the morning. Then, to use his own confession, he was ready to enjoy the "profundity of sleep."

He introduced military psychiatry in this country, was one of the first Superintendents to place female wards under women physicians, was one of the organizers of the Mental Hygiene movement, attended sessions and took conspicuous part in the activities of many medical societies. The positions and honors that came to him were not regarded as personal, they were concrete evidence that more and more the members of his own profession were recognizing the fact that psychiatry was an important branch of medical science, that the problem of the mind diseased must be kept close to the hearts of all physicians.

There was no spark of professional jealousy in his makeup. He was working for those less fortunately endowed, and all that he acquired was freely given to his associates. He was the recognized leader, but he labored shoulder to shoulder, hand in hand, and in genuine companionship with his co-workers.

When he passed on, it was noticeable that men and women in all walks of life, with no particular personal acquaintance with him but legion in numbers, mourned the loss of one whom they held in personal regard. Why should this be so? Why should persons whom he knew not by name nor by sight feel that they had sustained a loss? The answer lies in the fact that the people long since had been convinced of the sincerity of his desire and purpose to serve his fellow man.

His friend and personal counselor, Frederick A. Fenning of the Washington Bar, has collaborated in the preparation of this paper that expression may be given to some of the underlying motives, to a few of the purely personal aspects of one with whom he enjoyed intimate association for more than thirty-three years.

WILLIAM GERRY MORGAN, M D , F A C P ,
Secretary General

DR ELIAS HUDSON BARTLEY

Dr. Elias Hudson Bartley (Fellow), Brooklyn, N. Y., died January 12, 1937, of senility. Dr. Bartley was one of the Founders of the American College of Physicians, and, therefore, had been a Fellow since 1915. He was early elected a member of the Council, now known as the Board of Regents, of the College, and the early Minutes of the organization show that he took a very active part.

Dr. Bartley was born at Bartley, N. J., December 6, 1849, later removing to Princeton, Ill., where he attended the public schools. He received his Bachelor of Science degree from Cornell University in 1873, taught in the Princeton High School for a year and then became Professor of Chemistry at Swarthmore College, Swarthmore, Pa., for three years. He then pur-

sued his medical training at the Long Island College Hospital, graduating in 1879. Immediately thereafter he was appointed Assistant to the Chair of Diseases of Children, Lecturer in Chemistry and Instructor in Chemical Analysis at the Long Island College Hospital. He was promoted to the Professorship of Chemistry and Toxicology in 1886, continuing in that capacity until 1901. Coincident with this, he developed the Department of Pediatrics. He was professor in that department from 1901 to 1915. He was Acting Dean of the Faculty from 1915 to 1917, when he retired as Emeritus Professor of Chemistry and Pediatrics. He was Chief Chemist for the Brooklyn Health Department from 1882 to 1888, a member of the Kings County Board of Pharmacy from 1892 to 1898, and Consulting Pediatricist to the Long Island College Hospital, Methodist Hospital and the Kingston Avenue Hospital, all of Brooklyn, and the Southside Hospital, Bay Shore. For several years he was Chief of the Department of Pediatrics at the Brownsville and East New York Hospital. He was a member of the U. S. Pharmacopeia conventions in 1890, 1900, 1910 and 1930. During his term as Chief Chemist to the Health Department of Brooklyn he organized the first systematic attempt to inspect and control the milk supply of that city. This met with much opposition, but by persistent work and the building up of public sentiment, results began to be obtained. It is said that cholera infantum immediately decreased and finally disappeared. The results he obtained constitute a striking example of public health education backed by the medical profession. In 1902, through the efforts of the Medical Society of the County of Kings, the first Milk Commission was organized, with Dr. Bartley as its chairman. From 1892 to 1902 Dr. Bartley was Dean and Professor of Organic Chemistry at the Brooklyn College of Pharmacy.

The Long Island Medical Journal was founded by Dr. Bartley while he was President of the Associated Physicians of Long Island. In 1912 he was elected President of the Medical Society of the County of Kings. He was a member of the Medical Society of the State of New York, a Fellow of the American Medical Association and a member of its House of Delegates, 1909-10, a member of the New York Academy of Medicine, the Brooklyn Pediatric Society, the Brooklyn Pathological Society and many other organizations. In addition to his Fellowship and Councilorship in the American College of Physicians, he served at one time as a Vice President.

Dr. Bartley was the author of many published articles and of a "Text-book on Medical and Pharmaceutical Chemistry," of which seven editions appeared between 1885 and 1909. He was also the author of a "Manual of Clinical Chemistry," which was published in three succeeding editions.

Although of late years his contacts with the College and his activities have necessarily been diminished, the spirit of his service remains

DR JAMES P McKELVY

Suddenly stricken while en route to Arizona to spend the winter, Dr James P McKelvy of Pittsburgh, Pa, died in St Luke's Hospital, Kansas City, Missouri, on January 28, 1937

Born in Wilksburg, Pa, a suburb of Pittsburgh, December 1, 1869, his preliminary education was obtained at the local public schools and the Pittsburgh High School After graduation from the latter he studied chemistry at Columbia University and then returned to Pittsburgh to become associated with the manufacturing firm of McIntire-Hemphill Company as chemist

After three years Dr McKelvy returned to Columbia University to enter the College of Physicians and Surgeons, from which he graduated in 1901 He served internships for two years at the Roosevelt Hospital and the Sloan Maternity Hospital and then returned to Pittsburgh to take up the practice of medicine

Dr McKelvy was attending physician to the Allegheny General Hospital from 1907 to 1925 and Physician-in-Chief from 1925 until his death He was a member of the Board of Managers of the William H Singer Memorial Research Laboratory from the time of its establishment in 1916

President of the Allegheny County Medical Society in 1919, he was also a member of the Pennsylvania State Medical Society, a Fellow of the American Medical Association and the Pittsburgh Academy of Medicine Elected to Fellowship in the American College of Physicians in June 1917, he was almost a charter member of our organization

Dr McKelvy belonged to the Pittsburgh Club, Oakmont Country Club, Allegheny Country Club, Fox Chapel Country Club, University Club and the Seaview Golf Club of Absecon, N J

He was a member of the Sixth United Presbyterian Church of Pittsburgh

Surviving are his son, Mr William M McKelvy, a brother and three sisters

E BOSWORTH MCCREADY, M D, F A C P,
Governor for Western Pennsylvania

DR JAMES LESLIE BUSBY

Dr James Leslie Busby, a Fellow, died in Pasadena on February 18, 1937 Dr Busby was born in 1890 in Millersport, Ohio He received his M D degree from Ohio State University in 1913, was an intern in St Clair Hospital, Columbus, in 1913 and 1914 and practiced in Shelby and in Columbus from 1914 to 1918 when he joined the Medical Corps of the Army He was assistant chief medical advisor in the Bureau of War Risk Insurance and for two years chief of the section of medicine and surgery in the United States Public Health Service He entered the Mayo Foundation January 1, 1923 He was made an associate in medicine January 1, 1925, and was

an instructor in medicine from 1927 to 1929. He left the Mayo Foundation in August 1929 to practice medicine in Pasadena.

Dr. Busby was a member of the senior staff of the Los Angeles General Hospital and an Associate Professor of Medicine in the College of Medical Evangelists. He was a member of the American Medical Association, the Southern California Medical Association, the Los Angeles Clinical and Pathological Society, the Alumni Association of the Mayo Foundation for Education and Medical Research, and a Fellow of the American College of Physicians. He was on the staff of the Huntington Memorial Hospital and St. Luke's Hospital in Pasadena and chairman of the Medical Advisory Board of the Ruth Home in El Monte, California. Dr. Busby was widely and well known. He enjoyed a large practice and had many professional, civic, and social connections. He will be greatly missed in his community. He is survived by his wife, Louise Busby, and two children.

EGERTON L. CRISPIN, M.D., F.A.C.P.,
Los Angeles, California

DR. DAVID G. GHRIST

Dr. David G. Ghrist, a Fellow of the College, died in the Good Samaritan Hospital in Los Angeles on February 3, 1937, from pneumonia following an attack of influenza.

Dr. Ghrist was born in Ames, Iowa, in 1898. He received an A.B. degree from Stanford University in 1921 and an M.D. from Harvard University in 1925. He had an internship in the Los Angeles General Hospital from 1925 to 1926, which was followed by a period of private practice until April 1, 1927, at which time he entered the Mayo Foundation as a Fellow in Medicine. He was appointed a first assistant in his clinical division of medicine April 1, 1929. In 1930 he received a degree of Master of Science from the University of Minnesota.

Dr. Ghrist went from the Mayo Foundation to Los Angeles in October 1930, where he established himself in the practice of internal medicine. His training, ability, and personality enabled him to build up a large and satisfactory practice in his chosen field.

Dr. Ghrist was a member of the Beta Theta Pi and Nu Sigma Nu fraternities. He was a member of the Staff of the Good Samaritan Hospital and of St. Vincent's Hospital, and a member of the Association for the Study and Control of Rheumatic Diseases. He was Secretary and Treasurer of the Southern California Medical Association and was Associate Professor of Medicine in the University of Southern California Medical School.

Dr. Ghrist was an able physician whose sterling qualities were admired by all who knew him. He is survived by his widow, Winnefred Ghrist, and by one daughter.

EGERTON L. CRISPIN, M.D., F.A.C.P.,
Los Angeles, California

DR COLLINS HICKEY JOHNSTON

Dr Collins H Johnston (Fellow), died suddenly in his home, Grand Rapids, Michigan, on December 29, 1936. He was seventy-seven years old and was actively engaged in his professional work until the day of his death.

Born in Detroit, Michigan, he graduated from the University of Michigan (Lit.) 1881, (Medicine) 1883, and came to Grand Rapids a few years later. Throughout his busy life he maintained a great interest in the scientific side of medicine. A real student with excellent background, he kept up with the newer things in medicine throughout his long professional life, by means of frequent trips to teaching centers both in this country and abroad. A general practitioner, he had, at different periods, shown very special interest in Pediatrics and Tuberculosis. The special societies to which he belonged attest this interest. He was a member of the American Clinical and Climatological Association, Michigan Trudeau Society, Central States Pediatric Society, and others. At one time he was a member of the House of Delegates of the American Medical Association, and was an ex-president of the Kent County Medical Society. He was on the Visiting Staff of Blodgett Memorial Hospital and Honorary Chief of Staff of D. A. Blodgett Home for Children.

In civic affairs and in his church (Episcopal) he was always an active and willing worker, giving of himself willingly and untiringly. Measures for the promotion of public health always had his interest and for years he campaigned for a pure water supply, and was Chairman of the Medical Milk Commission for safe and good milk. He was largely responsible for the establishment of the Grand Rapids Clinic for Infant Feeding, one of the earliest clinics for this purpose established in the country.

Dr Johnston will be remembered by his colleagues as an aggressive, industrious and most competent practitioner. His constant, never failing effort to keep abreast of the times, his interest in all things pertaining to medicine, can well serve as a real example to the younger generation.

BURTON R. CORBUS, M.D., F.A.C.P.

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OF DOCTOR JOSEPH HERSEY PRATT

PROBLEMS OF ENDEMIC GOITER *

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THE two goiter conferences held at Berne in 1928 and 1933 revealed to the trained eyes of the participants the fact that in different countries, as, for example, in Munich, Berne, Vienna, Oslo and Utrecht, the clinical course and microscopic appearance of endemic goiter are quite variable. One dare not, for example, carry over and apply the experience of McCarrison or the Scandinavian countries to the endemic malady of the subalpine regions or, perhaps, the North American areas. The fundamental studies of the Swiss investigators and recently those of Dieterle and Eugster have shown that endemic goiter is locally confined to certain regions, villages and even houses. Further, it is not peculiar to the higher altitudes but rather occurs in the subalpine regions and gravelly areas about the streams which flow northward and southward from the Alps, as well as in the diluvial formations which represent deposits of the glacial epoch. Cretinism, the most baneful result of thyroid insufficiency, also occurs in the midst of this endemic goiter region. Endemic goiter in Europe is by no means entirely limited to the subalpine regions, for isolated areas where goiter is common are also found in Holland, along the North Sea coast, as well as in the valleys of the Oder, the Vistula and even the Saar. In the latter goiter areas, however, there is a striking absence of cretinism. The goiter which occurs in those endemic regions near the seacoast is, however, characterized by a great sensitiveness to iodine. Theodore Kocher has pointed out that true, genuine Basedow's disease occurs quite rarely in the subalpine endemic areas, while in the lowland plains of North Germany (i.e., in a country which is nearly free from goiter) it occurs not only much more frequently, but also in a much more malignant form. I have, myself, encountered the more acute forms of Basedow's disease which threaten the life of the patient, only in the regions of Northern Germany.

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Reports from the subalpine endemic regions indicate that even in new-born infants the thyroid glands are distinctly larger and heavier than those of the new-born in North Germany. Indeed, actual goiter occurs in the new-born in the subalpine regions. These thyroid enlargements of the new-born ordinarily present the picture of "parenchymatous" goiter, that is, with branching sacs rich in cells without follicle formation and without colloid. Further, experience has shown that even in endemic regions goiter of the new-born does not occur if the mother is given iodine during pregnancy. I possess such preparations of the thyroid gland of new-born infants from the endemic regions which were taken from children whose mothers had been treated with iodine and I was able to prove to my own satisfaction that in these cases the thyroid had a completely normal appearance, with follicles properly filled with colloid.

It is certain that endemic cretinism is closely associated with pathological changes in the thyroid gland. In about 90 per cent of the cases this takes the form of nodular goiter, often of considerable extent and showing severe degenerative changes. In about 10 per cent of the cases of cretinism there is no goiter, but rather we find almost complete absence of the thyroid. In these cases the thyroid gland is either quite undeveloped or, as the result of intra-uterine degenerative processes, it has been reduced to a small and compact solid mass. The most severe cases of cretinous degeneration are these with *athyrosis*.

It has further proved to be the case that in most cases of cretinism the mother likewise was goiterous. It cannot be concluded from this that both goiter and cretinism rest upon an inherited basis. The more probable conception is that the noxa of goiter, *the nature of which is unknown* to us, has acted during the course of the pregnancy, not only on the mother but also on the child in utero. As a consequence of our above mentioned experiences with the congenital goiter of the new-born, it may also be hoped that normal development of the thyroid gland may be achieved by means of the administration of iodine to pregnant women. In other words, the fight against cretinism must begin, not *after* the birth of the child, but rather while it is still in the uterus.

The administration of iodine to all women in the endemic areas is feasible only by means of the introduction of the use of iodized salt by the governmental authorities, for women frequently are unaware of a pregnancy and, further, the indolence of the inhabitants would prevent their carrying out iodine treatment of their own accord.

The question as to whether cretinism can actually be prevented by such radical measures is, however, still uncertain and the answer may never be known with certainty, more particularly because cretinism, for reasons unknown, has shown a substantial decrease during several decades.

In all the *milder* cases of cretinism, the condition is usually recognized first when the child enters school, at which time the waddling gait, the deeply depressed root of the nose and the defective intelligence become apparent.

At this time it is too late for iodine treatment, and the dried and powdered whole thyroid gland should be administered (not thyroxin), thereby very excellent results are often attained

During the *school age* there very often appears an enlargement of the thyroid in children of otherwise healthy appearance. This goiter of school age gradually increases in size during the next few years. The goiter of school age is quite common in the endemic areas, as, for example, in Berne or in the Algau, up to 80 per cent of all school children being affected. Experience shows this goiter of school age to be a harmless phenomenon which is almost never associated with signs of hyperthyroidism. It usually regresses spontaneously at the completion of puberty and responds exceedingly well to small doses of iodine. Because of this fact we have entirely given up the operative treatment of the goiters of school age and if such goiters become troublesome, they are treated with small doses of iodine, which may be given to the children by the school teacher in the form of iodosterin tablets, once a week. At about the twentieth year this adolescent goiter very often disappears entirely. Occasionally it persists to some degree, in which case the response to iodine is not nearly so good as is that of the true goiter of school age. At about the twenty-fifth year of life there often develops a certain hyperthyroid symptom complex. If, in the female sex, a pregnancy should occur at about the twentieth year, it is common for a swelling of the thyroid (as well as of the pituitary, as is well known) to become apparent. These *goiters of pregnancy* ordinarily are not accompanied by signs of either hypo- or hyperthyroidism and they usually react very favorably to small doses of iodine. *After* delivery they slowly regress during the subsequent weeks in the majority of cases and during this period the young mother at times notices weakness with tremulousness, physical and mental excitability and general loss of strength. This *asthema of young women* often seems to be associated with the shrinking in size of the thyroid gland, together with some hyperthyroidism. In other cases the goiter of pregnancy persists and develops into a nodular goiter.

Since the goiter of school age, or adolescent goiter, is a harmless affair and responds brilliantly to iodine, the question arises as to whether iodine therapy is necessary at this age and whether it offers a dependable protection in later life. Is it possible for us to say that iodine therapy during school age gives us any prospect of a prophylactic effect against the later development of goiter or hyperthyroidism? I cannot answer this question in the affirmative. Indeed, I recall a number of cases where a youthful goiter was treated with good results and later during the thirties or forties a goiter appeared in spite of this fact, requiring operative interference. Further, we are unable to assert that the reduction of adolescent goiter to normal size and function constitutes a protection against the later appearance of Basedow's disease or of an iodine hyperthyroidism.

In the case of Basedow's disease, which I am unable to distinguish symptomatically from the so-called *Struma Basedowifcata* or iodine hyper-

thyroidism, pre-operative preparation with Lugol's solution in doses which are not too small, in the manner introduced by Plummer, has shown itself to be of such value that at the present time it has been introduced in practically all surgical clinics. On the other hand, *prolonged* treatment of Basedow's disease with small doses of iodine, as recommended by Neisser, is rejected by most physicians and considered dangerous.

I conclude. In those regions of endemic goiter, in the midst of which cretinism is observed with a good deal of frequency, and indeed only in these, prophylaxis by means of the administration of iodine to pregnant women should be instituted by the authorities. This is certainly possible only through the substitution of iodized or complete salt for the ordinary table salt. In all other endemic goiter areas, on the other hand, the obligatory introduction of iodized salt is not desirable. The general use of iodized salt may be conducive to harm, in the case of older people or, particularly, to goiterous members of the family. The goiter of school age and adolescent goiter promptly regress under iodine therapy and almost never demand surgical interference. It is as yet, however, not certain whether the iodine treatment of adolescent goiter affords prophylactic protection in later life against the occurrence of goiter and hyperthyroidism.

BLOODY PLEURAL FLUID, AN UNUSUAL COMPLICATION OF CIRRHOSIS OF THE LIVER *

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A NOTE on an unusual clinical picture is not inappropriate for a Festschrift to Joseph H. Pratt, who always has been an exponent of the art of being interested in the very unusual as well as the very common disease combinations of man. He is and always has been a keen clinician with an extraordinarily complete knowledge of medical bibliography.

An accumulation of pleural fluid in combination with cirrhosis of the liver appears to be not very unusual. Rolleston and McNee¹ quote Vedel and Puech as estimating it to occur in one-seventh to one-sixth of all cases, more often on the right than on the left side, often, according to them, as a manifestation of concomitant tuberculosis. However, a search through the Quarterly Cumulative Index back to its beginning in 1916 yielded only four titles (Salvatore,² Vedel and Puech,³ Clerici⁴ and Cassarni⁵) indicating papers on pleural fluid in association with cirrhosis of the liver. None of these were accessible to the author.

For the pleural fluid in patients with cirrhosis of the liver to be bloody in nature seems to be extremely unusual, since in this period no title could be found under either cirrhosis of the liver or various forms of pleural disease indicative of hemorrhagic fluid in the pleura in combination with cirrhosis of the liver. Rolleston and McNee speak of such hemorrhagic pleurisy as being of tuberculous origin, citing Barjon and Henry⁶ and Jean⁷ and reporting a case of their own, or as the result of alcoholism (Fernet⁸), or caused by trauma, citing a patient of theirs. The only case I have been able to find, independent of these factors, is one cited by them as reported by Taylor⁹. Examination of Taylor's report shows that a child of 13 with cirrhosis of the liver causing ascites, frequently tapped, developed near the end of life right-sided pain and a pleuritic rub with paracentesis the next day of nine pints of fluid. Two days later she died, and autopsy showed five ounces of blood-stained serum in the right pleural cavity, no evidences of pleural or pulmonary tuberculosis, normal heart and nodular cirrhosis of the liver. Taylor's title was "Cirrhosis of the Liver in Children, with Some Remarks on Cirrhosis", here there is nothing to indicate description of so unusual a complication of cirrhosis of the liver, very probably other cases may have been reported equally buried under non-committal titles.

Recently I have had opportunity to observe a case of cirrhosis of the

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liver that, under observation, developed hemorrhagic pleural effusion requiring removal of paracentesis nine times before death.

The following gives the important data about this patient. A man of 60 entered the Peter Bent Brigham Hospital on November 13, 1936, complaining of jaundice of five weeks' duration and of enlargement of the abdomen of two weeks' duration. He had a history of excess in alcohol intake, no history of syphilis. He had been obese, now weighing 260 pounds after having lost 100 pounds in two years by dieting. Jaundice was marked, with dark urine and light stools for 11 days, and then cleared up to recur two weeks before admission, when his abdomen began to increase in size. On admission he was jaundiced (icteric index 70), obese with enlarged abdomen, dull in flanks and showing a fluid wave. His heart was not enlarged, there was a loud blowing systolic murmur over the precordium. Liver and spleen could not be palpated. Urine showed bile, at times albumin and very occasional cells and casts in sediment. Phthalein excretion was 90 per cent in 2 hours and 10 minutes, blood urea nitrogen 12 mg per cent, plasma protein 5.7 gm per cent with globulin 2.5 per cent and albumin 2.9 per cent. Blood showed a moderate anemia (85 per cent hemoglobin, 3,900,000 red cells) and a normal leukocyte count (7,800).

On December 7 physical signs of left-sided pleural fluid developed, and, on December 10, 900 cc of bloody, bile stained fluid were withdrawn, which had a specific gravity of 1.008 and contained 23,000 red and 2,000 white cells per cu mm, 35 per cent lymphocytes and 65 per cent polynuclears. Tapping of left chest yielded bloody fluid as follows: December 15, 1,200 cc, 21, 800 cc, 28, 2,400 cc, January 7, 2,000 cc, 12, 2,000 cc, 23, 3,400 cc, 25, 1,600 cc, the red cells progressively rising to 600,000 per cu mm. On January 22 abdominal paracentesis yielded 3,100 cc of straw yellow fluid. As is so common in cirrhosis of the liver, from time to time fever developed, again to disappear. There was no apparent relation of the fever to the hemorrhagic pleural fluid. The patient grew progressively worse, and after five days of terminal fever died on February 6, 1937. Four roentgen-rays of chest, the first on November 20, when there was but a small amount of fluid in the left chest, never showed anything more than fluid and poorly aerated lung. Sediments from all nine specimens of pleural fluid were studied by methods of fixation and tissue stains, in the third, the pathological department made a diagnosis of tumor cells, no tumor cells were seen in the other eight.

The diagnosis in this case, particularly after the development of the hemorrhagic fluid in the left pleural cavity with its rapid reaccumulation, was actively discussed by the staff. At first the diagnosis of cirrhosis of the liver was held. With pulmonary and pleural signs appearing, it was thought that these resulted from a complicating inflammation. When the pleural fluid was found bloody and reaccumulated so rapidly, diagnosis veered to neoplasm, presumably primary in liver, as none could be demonstrated else-

where (negative roentgen-ray study of gastrointestinal tract, no evidence of prostatic tumor)

However, at a public clinic on February 4 the author of this paper expressed unequivocally his belief that the hemorrhagic pleural fluid was a result of the cirrhosis and was not of neoplastic origin and that the patient had cirrhosis of the liver of alcoholic etiology, in which possibly some lobules had undergone transformation into neoplasm

The patient died two days following this clinic and autopsy revealed the correctness of the above diagnosis. There was no evidence that neoplasm or tuberculosis was responsible for the recurring hemorrhagic pleural fluid. The gastro-esophageal venous system did not appear abnormally dilated

SUMMARY

A case is reported of cirrhosis of the liver with recurrent left-sided bloody pleural fluid, the pleural condition not the result of neoplasm or tuberculosis

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THE GROWING IMPORTANCE OF CARDIAC NEUROSIS

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- I Introduction
- II Case histories of patients with cardiac neurosis, with and without heart disease
 - A Neurosis predominating
 - Case 1 *Neurosis Induced Largely by Neurocirculatory Asthenia Normal Heart*
 - Case 2 *Neurosis Initiated by Paroxysmal Tachycardia Normal Heart*
 - Case 3 *Neurosis Induced by Sudden Knowledge of Compensable Heart Disease While in Army Rheumatic Valvular Disease*
 - Case 4 *Neurosis Following Coronary Thrombosis*
 - B Heart disease predominating
 - Case 5 *Severe Coronary Heart Disease Masked by Psychoneurosis and Morphinism*
- III Summary and conclusions

I INTRODUCTION

THE more heart disease there is, and especially the more widespread the publicity about it, the more important becomes the problem of cardiac neurosis. In fact it has assumed almost first place in our practice. Every week at least and sometimes daily for a while there are cases that must be carefully studied and treated with this point in mind.

The cardiac neurosis to which we refer is not neurocirculatory asthenia, which is not a mental and perhaps not even fundamentally a nervous state. We might better designate what we mean as *cardiac psychoneurosis*. It consists essentially of fear or apprehension about the heart, and it may be very severe and crippling. It is essential in the practice of medicine to recognize and to treat this condition early, for a long established cardiac neurosis may be almost incurable. The condition is increasing in frequency and is probably missed more often than any other cardiac diagnosis. It is time we laid the proper emphasis upon it.

Cardiac neurosis is always based on some very definite exciting factor. The occurrence of heart disease, especially heart deaths, among family and friends or even simply reported in the newspapers under dramatic headlines may initiate a cardiac neurosis in a person who is ready for a neurosis of some sort. The finding by a physician of a heart murmur, trivial or not, of some disturbance of rhythm which may be insignificant, of hypertension, great or slight, or of actual heart disease may be the exciting spark. A roentgen-ray report may unduly emphasize some unusual detail or an elec-

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trocardiogram may show an artefact or some slight deviation from the usual normal. Subjective sensations may be the starting point—a disagreeable extrasystole, a paroxysm of tachycardia, the manifold symptoms of neuro-circulatory asthenia, sighing respiration, true dyspnea, angina pectoris, the prolonged pain of coronary thrombosis, and the various pains in the center or left side of the chest of noncardiac origin (due to cardiospasm, bursitis, muscle strain, and pleurisy among others).

It is not always appreciated that the family or friends of an individual suspected of having some heart trouble may become more fearful than the subject himself and actually need more attention from the physician. Only recently we have had the interesting experience of being consulted by a woman 60 years old without evidence of organic heart disease, who had travelled from a distance for relief of frequent crippling attacks of paroxysmal tachycardia which had not been adequately controlled by any kind of therapeutic measure that had been tried. No doubt the specific therapy that we advised may be equally unsatisfactory but one thing we did do, and that was to uncover and to help clear up the main difficulty, which was not heart disease itself, nor the paroxysmal tachycardia, nor even the patient's cardiac neurosis, but a rather severe neurosis of fear in several members of a large devoted family. This was the crux of the situation and the abolition of that fear should make a great difference in the attitude of the family toward her illness. Likewise, it is not uncommon to encounter cardiac neuroses in young people with or without heart disease, that have resulted from over-solicitude of anxious parents.

The most difficult cases of all are those with serious heart disease complicated by cardiac neurosis. It is a common experience in practice that nervous prostration or a severe cardiac psychoneurosis following coronary thrombosis, especially in physicians, is more difficult to treat than is the myocardial infarction itself.

We shall present herewith a few selected and striking examples of cardiac neurosis, with and without heart disease, four in whom the cardiac neurosis was the outstanding condition and, in contrast, one, with autopsy, in whom very extensive heart disease was for a long time masked by a psychoneurotic state. We have recently presented in the *Medical Clinics of North America*¹ several other cases illustrating cardiac neurosis in its various forms.

II CASE HISTORIES OF PATIENTS WITH CARDIAC NEUROSIS, WITH AND WITHOUT HEART DISEASE

A Neurosis Predominating

Case 1 Neurosis Induced Largely by Neurocirculatory Asthenia Normal Heart

A young unmarried teacher, aged 37 years, was examined by us on September 15, 1936. He had had scarlet fever at the age of thirteen. His father, a physician, is alive at 70 years of age, nine years after the onset of angina pectoris and seven years after coronary thrombosis, his mother, aged 66 years, is of a nervous disposition, has hypertension, and complains of much palpitation of the heart.

As a boy the patient noted that he could not keep up with his playmates because of palpitation and breathlessness. Consequently he avoided strenuous exertion and had always avoided it since. About 15 years ago he began to have some aching to the left and below the left nipple usually following exertion or nervousness, and often associated with rapid forcible palpitation. In 1930 he was seen briefly by one of us (who was caring for his father at the time) and found to have a normal heart and a blood pressure of 110 mm mercury systolic and 70 diastolic. One month later, in September 1930, following unusual strain at his work, a period of nervous exhaustion and collapse occurred, associated with rapid palpitation (pulse rate 125 to 130). He went to bed with this illness, made a good recovery, and by December 1930 he felt quite well.

During 1931 he was in good health and able to play 18 to 36 holes of golf without difficulty, but he constantly took good care of himself. In 1931 he began to smoke cigarettes in gradually increasing numbers so that over a period of three years he was smoking as many as 30 a day. In February 1934 he began to find himself breathless on exertion (two flights of stairs) and to have palpitation and tachycardia as before. These symptoms, as well as some heartache, had continued unabated. During the year preceding his visit to us, he had taken on more strenuous work, had smoked heavily, and had found it necessary to give up golf and all other forms of exercise. The past summer had been particularly strenuous with teaching and lecturing and he had been under tension most of the time. With the aggravation of his former symptoms there had also been, on several occasions, pain in the left lower chest noted while riding over rough roads. He had also observed momentary "stopping of the heart" followed by a forcible beat. In July 1936 he began to have heartache and palpitation on retiring at night or on awaking during the night, particularly when lying on the left side. On July 10, 1936, he consulted a physician who told him that he had beginning angina pectoris and prescribed aminophyllin which was not taken. This diagnosis aggravated his symptoms further, increased his nervousness, and frightened him to such an extent that he resigned from the college where he was teaching and returned home on August 5, 1936. After a few weeks of rest at home he felt improved but he remained so worried over his condition that he insisted on being seen two weeks ahead of his scheduled appointment.

Careful questioning revealed no history of substernal pain. He was uncertain about radiation to the left arm and scapula, but frankly admitted that he had been looking for such radiation because he had heard one of us inquire about the characteristic radiation of the pain of angina pectoris in his father's case (coronary disease). He had also had access to medical books in which he had read about angina pectoris. Many physicians had assured him that his heart was normal, but the one who told him he had angina pectoris left the most profound impression. He was much depressed, wanted to know if he should claim disability benefits, and the inference was in talking to him that he had come home to die. He had taken bromides off and on for six years.

Physical examination revealed a heavy set man in apparent good health. The heart was normal in size, sounds, and rhythm. There were no murmurs. The pulse rate was 95. The blood pressure measured 132 mm mercury systolic and 85 diastolic. Except for slight acne over the back there were no abnormal physical findings. The fluoroscopic examination and electrocardiogram were normal.

He was told that his heart was normal and given complete reassurance on this point along with advice to avoid fatigue of nervous origin, to limit tobacco to three or four cigarettes a day, to take only small amounts of coffee, and to exercise regularly.

When seen again on October 2, 1936, he reported that he had been completely well in the past two weeks since being reassured about his heart, that he had walked

as much as 10 miles a day, and that the pulse had been slower and the heart action quieter than for years. Physical examination again showed no abnormalities. The pulse was regular at a rate of 84. The blood pressure measured 120 mm mercury systolic and 80 diastolic. He was reassured further regarding his heart and advised to continue as before.

In November 1936 it was necessary to reassure him once more of the unimportance of several vascular naevi that he had found on his skin after reading a medical reprint in which mention was made of spots on the skin in heart disease. In the latter part of December he reported a recurrence of many of his old symptoms in mild form attributed to increased nervous tension. By curbing his activities for several weeks these symptoms disappeared, and he is now in the good state of health which he enjoyed last fall.

Discussion The factors in the background of the neurosis in this case are obvious, and it would have been surprising if, under the circumstances, a neurosis had not developed. In the first place, we are dealing with a nervous, sensitive individual with longstanding symptoms of neurocirculatory asthenia who had always protected himself from physical fatigue. Secondly, his family environment was such that heart trouble was ever in his mind, his father having had coronary disease for years, and his nervous mother having hypertension and heart symptoms. Moreover, he had ready access to medical books and journals. In the third place, he had been working recently under much nervous tension. Fourthly, he was a heavy smoker and it is common for the excessive use of tobacco to render a person more heart-conscious. And finally, and most important of all, he was badly frightened by an apparently "snap" diagnosis of angina pectoris made by a physician who was not well acquainted with him.

In treatment this case illustrates the good result of complete reassurance about the heart and sympathetic advice concerning his condition and mode of life. In such a patient, for a while at least, repeated doses of reassurance are usually needed, but always a careful and complete examination is essential at the start.

Case 2 Neurosis Initiated by Paroxysmal Tachycardia Normal Heart

A 46 year old native housewife was first seen by us on February 17, 1936. Her family history was irrelevant. Her past history was unimportant except as it related to the present illness.

Fifteen years previously, about two months following the death of her only child, she was suddenly awakened one night by very rapid racing of the heart accompanied by severe pain in her left anterior chest. The pain was sharp and catching in character, was localized to an area about two centimeters in diameter over the fourth left costal cartilage, and was treated by the hypodermic injection of morphia. Following this, similar attacks of pain continued to occur at intervals of two to four weeks and were unrelated to exertion, emotional excitement, posture, meals, or respiration (except that during the pain she was unable to take a deep breath). The duration of the pain was from one minute to one hour, usually 15 to 30 minutes, and there was no radiation.

Relief usually followed the administration of morphia which had been given subcutaneously or by mouth for nearly every attack of pain. Nitroglycerine had

been tried but found ineffective. In December 1933 a brother, to whom she was much attached, died. Immediately thereafter her attacks of pain increased in frequency and severity so that she was confined to bed for 10 weeks. Since that time, over a period of about two years, she had had two to three attacks of "agonizing" pain daily, each requiring morphine ($\frac{1}{4}$ to $\frac{1}{2}$ gr) for relief. Also during this time occasionally she had a sensation of fullness in her throat and palpitation. These symptoms frightened her and were attended by breathlessness and flushing of the skin.

From April 1935 to January 1936 she was under the care of a physician who was able to bring about some improvement with reassurance, phenobarbital, quinine, and belladonna, and a reduction diet, but there were two marked exacerbations of symptoms in October 1935 and again in December 1935. It was at the latter time that she began to complain of oppression or constriction beneath the sternum, directly following the attacks of acute pain described above, and thought by the patient to have been relieved after 15 minutes by nitroglycerine. She complained now also of sharp discomfort in the region of the right scapula "like the pain of pleurisy" coming and going at times during the acute pain. Among other things she had been troubled by diarrhea for a "number of years." This had been aggravated by quinine, but cleared up following the administration of dilute hydrochloric acid.

Repeated examinations by competent men failed to reveal any significant abnormality of the heart or nervous system and after 15 years of symptoms her general health remained unimpaired. Although the consensus among those who saw her was that her symptoms were functional in origin and aggravated by addiction to morphine, it was also agreed that she should be studied with the possibility of paravertebral alcohol injection of the thoracic sympathetic ganglia as a means of relieving her paroxysms of pain. Accordingly she entered the hospital under the care of Dr J C White.

Physical examination on entry revealed a slightly obese woman, apparently well. The pulse was regular at a rate of 84. The blood pressure measured 118 mm mercury systolic and 94 diastolic. The heart was normal in size and sounds. There were no murmurs. The examination showed no abnormalities except for quite marked precordial tenderness on light palpation.

The urine, blood, and stools were normal. A lumbar puncture revealed normal dynamics and a normal spinal fluid. The spinal fluid Wassermann was negative. The Hinton reaction of the blood was negative. The basal metabolic rate was minus 3 per cent. The electrocardiogram was normal except for slight left axis deviation consistent with her build. Roentgen-ray examination of the heart and lungs and of the dorsal vertebrae revealed no abnormality. A Graham test for gall-bladder disease was negative.

While under observation, many of her attacks coincided with visits by the attending physicians. A typical severe attack as observed by one of us was as follows. At the onset, she grasped the area beneath her left breast with her left hand and rocked back and forth groaning with pain. Respirations became deep and rapid. From her breasts up the skin became deeply flushed, and there was some mottling in the flanks, but the lower extremities were not involved. The temperature and sweating of the extremities were normal, but she perspired a great deal over the face and chest from increased exertion. Breathing later became shallow but remained forceful and rapid. The pupils remained intermediate in position. While listening to the heart over a period of three minutes the rate varied from 100 while holding her breath to 180 while at the height of a fit of sobbing and moaning. However, there seemed to be no relation between the severity of the pain, as manifested by her reaction, and the rate of the heart. At times she complained just as bitterly when the rate was 120 as when it was 180. The rhythm was regular throughout.

The blood pressure at the height of the attack measured 200 mm mercury systolic and 100 diastolic. A $\frac{1}{4}$ grain dose of morphia quieted her within a few minutes and the pulse rate dropped to 100 with slight increases up to 120 as her sobbing and moaning gradually ceased. Forty-five minutes after the onset of the attack she was still holding her breast as if it ached but she was quiet and the pulse rate was 88. An electrocardiogram during the attack showed sinoauricular tachycardia, rate 130.

On February 19, 1936, Dr. J. C. White performed a left paravertebral novocaine block from the third to the sixth dorsal sympathetic ganglia, including the visceral ramus, which gave good anesthesia over the area where she complained of pain. However, within $2\frac{1}{2}$ hours, as sensation returned, she had another severe attack of pain, proving that her pain was not visceral in origin, because, under these circumstances, pain is consistently relieved for 24 hours or longer. Two days later the area of painful sensation in her chest wall was injected with novocaine during an attack, but without relief of the pain. Having thus demonstrated the futility of any neurosurgical procedure for the relief of her pain psychiatric treatment was recommended.

On September 15, 1936, her physician reported that after several months of sanatorium care her morphine addiction had been broken and that her precordial pain had nearly disappeared. She was doing nicely with an occasional placebo.

Discussion This case is one of the utmost importance, for it represents a group of patients who have been unsatisfactorily diagnosed and handled. Her present illness dating back 15 years began apparently with a paroxysm of tachycardia attended by severe chest pain which awakened her one night shortly after the death of her only child. With this very first attack morphine was given and without careful analysis each succeeding attack was diagnosed as possible angina pectoris unrelieved except by morphine. In the first place it should have been quickly obvious that angina pectoris does not occur like this in a young woman and in the second place that angina pectoris does not require morphine. It is, of course, also important to note that nitroglycerine had been tried and found ineffective. A clue late in her disease was the exacerbation of her symptoms following the death of her brother to whom she was much attached.

It is quite probable, in fact certain, from our observations, that at least some and probably most of the so-called heart attacks were not of the nature either of paroxysmal tachycardia or angina pectoris. Early in her experience she had doubtless become sensitized by her original attack or attacks of paroxysmal tachycardia to any elevation of heart rate or increased force of heart action due to effort or excitement which would bring on a "heart attack" requiring morphine. The reaction in her case to any tachycardia might be considered a conditioned reflex. Repeated normal physical examinations and electrocardiograms made very unlikely a diagnosis of heart disease sufficiently serious to incapacitate her.

The most important factor of all in maintaining the prolonged psychoneurotic state was certainly the morphine therapy. She had become an addict. With morphine in the foreground, the background must always remain obscured no matter what the disease condition may be. The hysterical nature of the attacks with rapid relief by morphine bears witness to this.

Finally, the failure of the sympathetic and peripheral novocaine nerve block to relieve the attacks proves their hysterical foundation.

The cure of her morphine addiction has already resulted in improvement but emotionally she is still far from normal

Case 3 Numbness Induced by Sudden Knowledge of Compensable Heart Disease while in Army Rheumatic Valvular Disease

A 29 year old native baker's helper who had not worked for 10 years on account of his health, was admitted to the Massachusetts General Hospital on March 14, 1936, complaining of attacks of precordial pain. He had had measles, mumps, and whooping cough in childhood, without significant complications. His appendix was removed in 1925 and the tonsils and adenoids were taken out in 1929. There was no history of rheumatic fever or chorea. He had smoked two packages of cigarettes daily until a short time before his entry to the hospital. One brother, a policeman, had been killed, another brother had died following the World War as a result of being gassed.

In 1926, while an enlisted man in the army, he had influenza, shortly following this illness he was declared completely disabled, because of heart trouble, by army physicians and given a medical discharge and a pension. One year later, in 1927, he began to have attacks of rather severe precordial pain, occurring once or twice a day, which he described as follows. The pain originated in the region of the apex of the heart, was dull, aching, and penetrating in character, radiated to the left shoulder and down the left arm to the hand, to the left chest posteriorly, and down the left leg to the knee. The attacks were of one to two hours' duration, were unrelated to effort, meals, or excitement, and were not relieved by nitroglycerine. Occasionally he was awakened at night by an attack of pain. In 1933, shortly after his government pension was entirely withdrawn, there was a sharp increase in the severity of his symptoms, which continued unabated coincident with his efforts to become reinstated on the pension list. In addition he began to notice moderate dyspnea, and rapid irregular palpitation on exertion, and with his attacks of pain. He had several severe nose bleeds in quick succession but no subsequent ones. For two years prior to admission he had had sudden syncopal attacks of unknown duration, occurring every three or four weeks, and followed for a short time by dizziness. He could suggest no precipitating factor for these attacks. For one year he had noticed slight pitting edema of the feet when he had been standing for an unusual length of time. For six weeks there had been fairly persistent nausea, he had vomited several times, and on three or four occasions he had suffered from severe frontal headaches lasting half a day. There was no orthopnea or cough.

Physical examination revealed a well developed and fairly well nourished young man with cyanotic lips. Breathing was normal. The heart was enlarged both to the right and to the left, the apex impulse lying in the midaxillary line, the right border of dullness $5\frac{1}{2}$ cm to the right of the midsternum in the fourth intercostal space. The heart action was forceful and the rhythm totally irregular. The rate was 80 at the apex and at the wrist. There were a Corrigan pulse and pistol-shot sounds over the peripheral arteries. At the apex there was a loud prolonged diastolic murmur, a loud slapping first sound, and a short blowing systolic murmur of moderate intensity. Fairly loud systolic and diastolic murmurs were heard at the aortic area and along the left sternal border. The aortic second sound was accentuated and greater than the pulmonic second sound. The blood pressure measured 140 to 120 mm mercury systolic and 60 to 50 diastolic. The lungs were clear. The liver edge was just palpable beneath the costal margin and slightly tender. There was no edema of the extremities.

The urine, blood, and stools were normal. The Hinton reaction was negative. A teleroentgenogram showed dilatation of the heart slightly to the left and markedly

to the right. Oblique views showed marked prominence of the left auricle posteriorly and some prominence of the left ventricle posteriorly. There was also marked enlargement of the right ventricle. The aorta was small, the pulmonary vessels were only slightly prominent.

These findings we interpreted as those of mitral stenosis and regurgitation combined with an aortic lesion (aortic stenosis and regurgitation). The electrocardiogram showed auricular fibrillation, ventricular rate 80, slightly widened QRS waves (early intraventricular block), a tendency to right axis deviation, and a normal chest lead.

The consensus among most of the observers who saw him had been that his pain was that of angina pectoris of the type sometimes seen in patients with rheumatic heart disease and extensive aortic regurgitation, notwithstanding the fact that the mitral valve involvement seemed preponderant in this case. He continued to have attacks of pain while in bed under observation and over a period of two weeks he was given morphia rather freely for relief. On account of the severity of his pain paravertebral alcohol injection of the upper left dorsal sympathetic ganglia seemed justified to some of the observers. This procedure was carried out with some difficulty on account of unusually wide and thick transverse processes of the vertebrae, but finally, after three attempts, the first to the fifth left dorsal ganglia were satisfactorily injected. The resulting anesthesia over the left chest and vasodilation of the left arm and hand indicated a sympathetic block, which, in the experience of Dr. J. C. White, had usually been adequate to relieve pain in cases of true angina pectoris. However, the attacks of pain continued as before and it then became evident that he did not have angina pectoris.

In reconstructing the case at the time of our first examination after the events recorded above it was apparent that he was having an extreme reaction to the precordial discomfort induced by a very large heart thumping against his chest wall. There were good reasons for considering psychoneurosis as the chief diagnosis superimposed upon a background of organic heart disease. He had received a pension from the government for years and when this was discontinued his trouble increased. His pain was atypical of true angina pectoris, originating mainly in the region of the cardiac apex where the heart displaces the ribs, radiating even to the left leg, lasting for hours, unrelieved by nitroglycerine, and often requiring morphia for relief. His heart did not show the marked aortic regurgitation which has been almost invariably present in cases of angina pectoris in young persons with valvular heart disease and finally, alcohol injection of the upper dorsal sympathetic ganglia on the left gave no relief. This opinion is further borne out by the fact that he has continued unimproved since his discharge from the hospital.

Discussion The neurosis in this patient was precipitated by the belated discovery of rheumatic heart disease when the patient was convalescing from a respiratory infection while in military service, and the importance of which was at once magnified by his immediate discharge from the service on pension. Any cardiac symptoms which this man had thereafter were naturally interpreted as serious.

The next step in his medical history was the marked exacerbation of his dolor pectoris following the withdrawal of his pension.

Then came the unfortunate label of angina pectoris to cripple him still more and, finally, to complete the picture there was the serious therapy consisting not only of morphine but also of the nerve injections. Confirmation of the diagnosis of psychoneurosis came with the failure of the nerve injections to give adequate relief.

Much time, money, and suffering could have been spared in this case by early recognition of the psychoneurosis and its proper treatment, chiefly by psychotherapy. It seems likely that even now the most effective measure would be the restoration of his pension. Such a thing as precordial rib resection might perhaps be advocated to give him subjective relief, but that is as yet an experimental measure.

Case 4 Neurosis Following Coronary Thrombosis

A 58 year old physician and naturalist was first seen by us on September 25, 1934, complaining of precordial oppression on effort. He had always had a "sensitive digestive tract" characterized by intestinal stasis and "auto-intoxication," but nevertheless he had been generally well and active. He had had pyelitis five years previously and severe whooping cough two years previously. He had used alcohol and tobacco heavily in years past, but both quite sparingly in recent months. He was overweight and had gained a few additional pounds recently. His father died of heart disease at the age of 46 years, his mother died of a "stroke" at 73 years of age.

For three and one-half years he had noticed on effort after meals an oppression in the left upper chest anteriorly radiating to the left shoulder and sometimes to the jaw, and relieved within a few minutes by resting. This symptom was somewhat worse after an attack of grippe nine months previously.

In May 1934 four months before his visit to us, he was awakened at 5:30 one morning by an attack of the chest oppression described above, which was, however, more severe than usual, lasting five hours and requiring morphine for relief. He had a slight fever for several days, the blood pressure fell to 85 systolic, and the white blood cell count on one occasion shortly after the onset of these symptoms was 18,000. He spent three weeks in bed and then gradually got up and about. On July 5, 1934, six weeks after the onset of the prolonged pain, the blood pressure measured 125 mm mercury systolic and 80 diastolic and a loud, late systolic murmur was heard at the cardiac apex by a consulting physician. The electrocardiogram at that time showed normal rhythm, rate 70, low voltage, late inversion of the T-waves in Leads II and III, and a normal Lead IV, altogether typical of myocardial infarction of the posterior or basal type. During his convalescence he had three or four brief attacks of chest oppression but none during the month preceding his visit to us. He felt well except for extreme nervousness and fearful apprehension about the consequences of his illness. He was afraid to be alone and insisted upon the constant presence and attentions of his wife. Because he had always led a fairly vigorous, physically active outdoor life, which he was now unable to do, his outlook was gloomy and he chose to look upon himself as entirely crippled and unable to carry on usefully.

Physical examination revealed a heavy set man in apparent good health, but somewhat nervous and apprehensive. The heart was normal in size, sounds, and rhythm. At the apex there was a slight late apical systolic murmur. The pulse rate was 80. The blood pressure measured 122 mm mercury systolic and 80 diastolic. The lungs, abdomen, and extremities were normal. Fluoroscopic examination showed the heart to be normal in size and shape and the lung fields clear. The electrocardiogram showed normal rhythm, rate 85, low voltage, and low upright T-waves in the conventional leads, a very definite improvement as compared to the original electrocardiogram in July 1934.

It was apparent that he had done well following his coronary thrombosis and that the basis of most of his existing symptoms was fear and apprehension. He was therefore strongly reassured regarding his heart, advised to resume some of his hunting and exploration but to avoid strenuous effort, to spend his winters in an

equable climate, and to carry nitroglycerine with him should the occasion arise for its use

He has been seen at intervals of six months since his first visit. During that time with much reassurance he has shown steady improvement and has been able to resume much of his former activity in his nature work outdoors. He still has some oppression in his chest on effort, particularly after meals or when nervous or fatigued, but he is able to get along quite well when he avoids exercise after meals and nervous tension. His physical, fluoroscopic, and electrocardiographic findings have remained much the same over a period of two and one half years. His mental attitude has improved greatly.

Discussion Little or no discussion is required in this case. One need only emphasize that coronary thrombosis, no matter how mild, is very commonly accompanied and followed by mental depression and fear especially in a physician. This tendency is likely to decrease rapidly in the future with the current discovery of many cases with small infarcts, long survival, and unhampered physical reserve. This case illustrates also the value of some other interest than the particular occupation of the individual, some interest which is not fatiguing and which may continue to be cultivated for years.

B Heart Disease Predominating

Case 5 Severe Coronary Heart Disease Masked by Psychoneurosis and Morphinism

A 34 year old manufacturer was seen by us on May 21, 1934. He had always led a strenuous life, smoked heavily, and had been under much nervous strain for years with family and community activities. He had had numerous illnesses and operations (appendix, tonsils, antrum, injured hands, and "adhesions"). In 1930 he began to take morphine for migraine and later it was necessary for him to take the cure at a sanatorium.

His father and mother died of heart trouble at the ages of 59 and 48 years respectively.

In July 1933 he strained himself holding back a car on a hill and was exhausted. He felt no pain then but on the following day his chest was lame in front and on the left side. Four days later he felt well and pitched hard in a ball game for seven innings, having to stop because of fatigue, and not because of pain. He was unable to play much golf for the next few days because of exhaustion. He then took a long train trip and two weeks after the ball game, while lifting his small son on the beach, he suddenly felt oppressive pain to the left of the upper sternum lasting five to ten minutes. This pain recurred at intervals throughout the day with increasing severity and duration until 9:30 p.m. when it became constant and required morphine, which gave him relief when given at 3 a.m. the following morning. An electrocardiogram taken several weeks after this episode showed definite evidence of myocardial infarction at the apex of the left ventricle.

After a prolonged convalescence with gradually increasing activity he returned to his former strenuous life about May 1, 1934. On resuming his usual activities he began to have sharp stabs of precordial pain several times daily at rest or on effort. When first seen by one of us he was under treatment for a renewed addiction to opiates.

On physical examination he appeared well but nervous and apprehensive. There was slight cardiac enlargement, confirmed by fluoroscopy. The heart sounds were

good, the rhythm regular except for an occasional premature beat, and there were no murmurs. The pulse rate was 90, the blood pressure measured 120 systolic and 75 diastolic. The electrocardiogram showed normal rhythm, rate 105, interrupted by one ventricular premature beat, flat T-waves in Lead I, and slight left axis deviation. A later electrocardiogram in September 1936 showed also an absent Q-wave in Lead IV, further confirmatory evidence of previous myocardial infarction.

It was the opinion of some of his medical observers that in spite of the definite evidence of coronary disease much of the precordial pain of which he complained was on a neurotic basis. After repeated medical investigations and prolonged rest without sufficient relief to allow him to carry on a comfortable and useful existence a diagnostic paravertebral novocaine injection of the upper dorsal sympathetic ganglia was done during one of his severe episodes of pain with almost complete relief within five minutes. He was so impressed with the relief obtained that he wished to have a resection of the sympathetic nerves no matter what the risk. This was attempted but he did not survive the operation. Postmortem examination disclosed extensive coronary sclerosis with old occlusion of the descending branch and thrombosis of the circumflex branch of the left coronary artery together with marked scarring of the left ventricle. There was a definite and pronounced aneurysmal dilatation of the anterior wall and apex of the left ventricle.

Discussion This case is of the greatest interest and importance and without its inclusion our paper would be open to serious objection. It presents the other side of the picture from that illustrated in the first four cases. With a renewed enthusiasm in the recognition and treatment of cardiac neurosis one may easily go too far and fail to recognize the presence of serious heart disease that may lead to early death.

This patient's coronary disease was in large part overlooked or minimized for several reasons, consisting of his youth, his obvious nervousness, his addiction to morphine, and his relatively normal physical examinations. The electrocardiogram, however, proved to be of vital importance as it has been in most of our other cases of coronary disease in youth. It showed, without question, the presence of extensive myocardial infarction which was later confirmed at autopsy.

The case illustrates, incidentally, the danger of radical neurosurgery, in the presence of severe coronary disease, in contrast to nerve injections.

III SUMMARY AND CONCLUSIONS

The growing importance of cardiac neurosis has impressed us with the need of its emphasis at the present day when there is so much publicity about heart disease. Every patient with cardiac symptoms or signs or with knowledge of heart disease in family or friends is a potential cardiac neurotic.

We have presented herewith five striking examples of cardiac neurosis. The first case had as a basis a hypersensitive nervous system, a history of heart disease in the family, access to medical literature, increased nervous tension in his work, and a hasty incorrect diagnosis of angina pectoris, the excessive use of tobacco may have been an aggravating factor. The second case was a young woman whose first heart attack, apparently consisting

of paroxysmal tachycardia with precordial distress, followed the death of her only child and was unfortunately treated with morphine, during the next 15 years she became a morphine addict and never showed any evidence of heart disease. The third case was a young soldier whose rheumatic heart disease was unfortunately discovered for the first time when he was suffering from neurocirculatory asthenia following influenza, and for which he was discharged as partially disabled from the army, an exacerbation of his symptoms followed some years later when his pension was discontinued and became so severe that it was confused with angina pectoris and treated with morphine and nerve injections. The fourth case is an illustration of the mental depression and neurotic apprehension which often follows coronary thrombosis, the patient was a middle-aged physician who made a striking gain after reassurance and the readjustment of his activities and interests.

It is obvious that the early recognition and proper treatment of cardiac neurosis by psychotherapy would have spared these four patients much time, money, and suffering. There are many other cases like these.

In contrast with these four cases we have presented one important example, case 5, of serious heart disease consisting of coronary thrombosis and myocardial infarction masked by psychoneurosis and morphinism in a young man whose electrocardiograms gave the necessary clues to the correct diagnosis.

REFERENCE

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AORTIC STENOSIS WITH SPECIAL REFERENCE TO ANGINA PECTORIS AND SYNCOPE [†]

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INTRODUCTION

THE accuracy of diagnosis, the interpretation of physical findings and the etiology, frequency and symptomatology of aortic stenosis have been matters of considerable controversy in recent years. About 30 years ago the diagnosis was often made on the basis of a systolic murmur over the aortic area without any other confirmatory evidence. It became particularly clear during the great war that this was entirely insufficient evidence to warrant the diagnosis, when in some army camps and in the hands of some boards that were examining recruits, large numbers of cases of aortic stenosis were being reported. Such cases were subsequently regarded as having neuro-circulatory asthenia, showing a basal systolic murmur frequently found in this condition. The result of this experience led to the view that still prevails in the minds of many, that aortic stenosis is rare. It will be clear from this study that the pendulum has swung much too far in this direction, and that many clinical aspects of aortic stenosis need reconsideration and reappraisal. Certainly it can be stated at the outset that aortic stenosis is a fairly common lesion, and that basal systolic murmurs cannot be dismissed lightly.

The purpose of this study is to review some of the clinical features of aortic stenosis that might help in diagnosis, and especially to discuss two complications to which attention has recently been called, i.e. the occurrence of syncope and angina pectoris.

Although there are numerous isolated references to aortic stenosis in the older literature briefly reviewed by Marvin ¹ and Margolies, ² it is only in the last decade that the importance of this lesion has been stressed. Cabot ³ in 1926 reported 28 autopsied cases. He called attention to the greater frequency of aortic stenosis in the male sex, the absence of evidence of aortic regurgitation in approximately half of the cases, and the occurrence of the disease predominantly in individuals past 40 years of age. Willius ⁴ studied 96 cases, and stressed the fact that anginal pain was a common occurrence in 21 per cent of his cases. Forty-six per cent also gave a clear cut history of rheumatic fever. Margolies ² emphasized the frequency of calcification of the valve in aortic stenosis but regarded the process in the most part as

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sclerotic in nature Christian⁵ reported 57 cases that came to autopsy, 21 of which had calcification of the aortic valve. He also predicted that the calcification could be visualized by the roentgen-ray. McGinn and White⁶ reviewed 123 cases of aortic stenosis that came to autopsy and 113 that were examined clinically. Only one-third of the cases that came to autopsy were accurately diagnosed during life. A definite history of rheumatic fever was obtained in 23 per cent of the autopsied group and 46 per cent of the clinical series. Faintness, dizziness or actual syncope were fairly common complaints, occurring in 22 per cent of the cases. Nineteen per cent had angina pectoris. Nine of the patients in their series died suddenly.

Marvin and Sullivan¹ reported 11 cases of aortic stenosis that died suddenly and presented the view that syncope and sudden death in cases of aortic stenosis may be due to a hypersensitive carotid sinus. Boas⁷ discussed 19 cases, four of which had angina pectoris, and believed that the angina pectoris was due to the narrowing of the aortic valve. LaPlace⁸ reported a series of cases of aortic valve disease and found that the degree of aortic regurgitation as measured by the diastolic pressure had no relationship to the presence of angina pectoris.

MATERIAL IN THIS STUDY

In the selection of material for this review only those cases were included that could be regarded as having definite evidence of aortic stenosis. The three main criteria were the presence of a systolic thrill at the base of the heart, the detection of calcification in the aortic valve on fluoroscopic examination and the postmortem findings. All cases that had definite evidence of organic involvement of the mitral valve were excluded in order to study the features of aortic stenosis per se, eliminating any complicating events that the presence of mitral valve disease might entail. For this purpose all the clinical and pathological data in the records of the Peter Bent Brigham Hospital, from the year 1913 to 1935 inclusive, were analyzed together with the cases seen by one of us in private consultation practice. This comprised a group of 180 definite cases of aortic stenosis.

ETIOLOGICAL CONSIDERATIONS

It has been and still is often difficult to establish a conclusive relationship between an early rheumatic infection and a subsequent valvular lesion. There is no indisputable and constant pathological finding which determines the rheumatic nature of any cardiac abnormality. The presence of Aschoff nodules in the heart, although very distinctive, is often wanting, even when there is every reason to believe that the lesion is rheumatic. An early rheumatic infection may have taken on one of the many bizarre forms so that the proper diagnosis never was made. Even when the correct diagnosis was made the patient and his family may not have been informed of it. When a great many years elapse, as often happens, before cardiac embarrassment develops, the early diagnosis may readily be forgotten. Finally

a positive past history of a rheumatic infection and the presence of a valve lesion is not necessarily proof that the former is the cause of the latter. One is therefore left with opinions rather than with proof.

If specific diseases from a clinical point of view are rarely if ever associated with the subsequent development of stenosis of the aortic valve, it is reasonable to eliminate them entirely from our discussion of causation. In this group may be included pneumonia, typhoid fever, syphilis, and many other specific infections. It may be mentioned at this point that we did not find a single instance in which aortic stenosis could have been due to syphilis, notwithstanding the great frequency with which this disease produces aortic insufficiency and aortitis. It is not certain, however, how often nonspecific infections of a mild degree such as the "common cold," influenza or sore throat were the etiological cause of cases included in this study.

The great frequency of calcification of the aortic cusps naturally led to the belief in the past that in many instances it was purely arteriosclerotic. This opinion seemed to be further validated, in many instances, by the absence of any previous history of rheumatism or of any other significant infections. In refutation one might offer the evidence that is found in the mitral valve. Here stenosis occurs and is frequently accompanied by marked calcification, even in comparatively young people in whom very few would deny the rheumatic etiology. This often occurs when there is no available history of previous rheumatism. In fact it is a common experience to find calcification developing in any old and prolonged inflammatory process like tuberculosis, syphilis, parasitic cysts and other conditions. From the above considerations it follows that a particular lesion of the heart may be regarded as rheumatic in origin if an early history of rheumatic fever, chorea, or other stigmata of rheumatic disease are present in a large percentage of the cases, and if there is no other predominating etiological cause. It is well to recall that in a large series of cases of mitral stenosis, which all regard as almost invariably due to rheumatism, a history of this early infection can only be obtained in slightly more than 50 per cent of the cases. If a similar incidence can be found in relation to any other valve lesion it is equally logical to assume that rheumatic fever is the etiological factor.

In this series of 180 cases there was a definite history of rheumatic fever or chorea in 57 instances (31.7 per cent). The figures for the two sexes were approximately the same. The interval between the first rheumatic infection and the time these patients were first examined averaged 23.3 years for the females and 28.9 years for the males. The extremes were quite wide, from a few years to 60 years. This is considerably longer than similar figures would be for cases of mitral stenosis. In addition there were 23 in which the history was questionable. By this is meant that there was a history of previous "rheumatism," sciatica, growing pains, nosebleeds, etc., or that a heart murmur developed after an early acute infection. If these are included the total incidence would be 44.4 per cent. This corresponds fairly closely to the observations of Willius⁴ who found a history

of rheumatic fever in 46 per cent of 96 cases of aortic stenosis. It is a somewhat lower figure than the 50 per cent that is generally found in cases of mitral stenosis. The difference in the two groups can readily be explained by the fact that aortic cases when detected are on the average 10 years older than those with mitral disease, the latter coming to a physician earlier in their course because of troublesome symptoms of congestive failure. The result is that the aortic cases have more frequently forgotten their early infections or these infections have occurred in an era when rheumatic fever was not so well understood.

From the above discussion it would seem logical to conclude that rheumatic fever is the most frequent and most important cause of aortic stenosis. Furthermore, we are of the opinion that arteriosclerosis and calcification are secondary manifestations superimposed on lesions due to rheumatic fever or to some other early nonspecific apparently mild infection.

AGE AND SEX

The age distribution in this group of 180 cases of pure aortic stenosis ranged from 13 to 81 years, with an average of 52.5 years. There were 108 males and 72 females, i.e. 60 per cent and 40 per cent respectively. The average age of the males was 53.6 years and of the females 51.4 years. There was no significant difference in the distribution of the two sexes in the various decades (figure 1) although the largest number occurred in

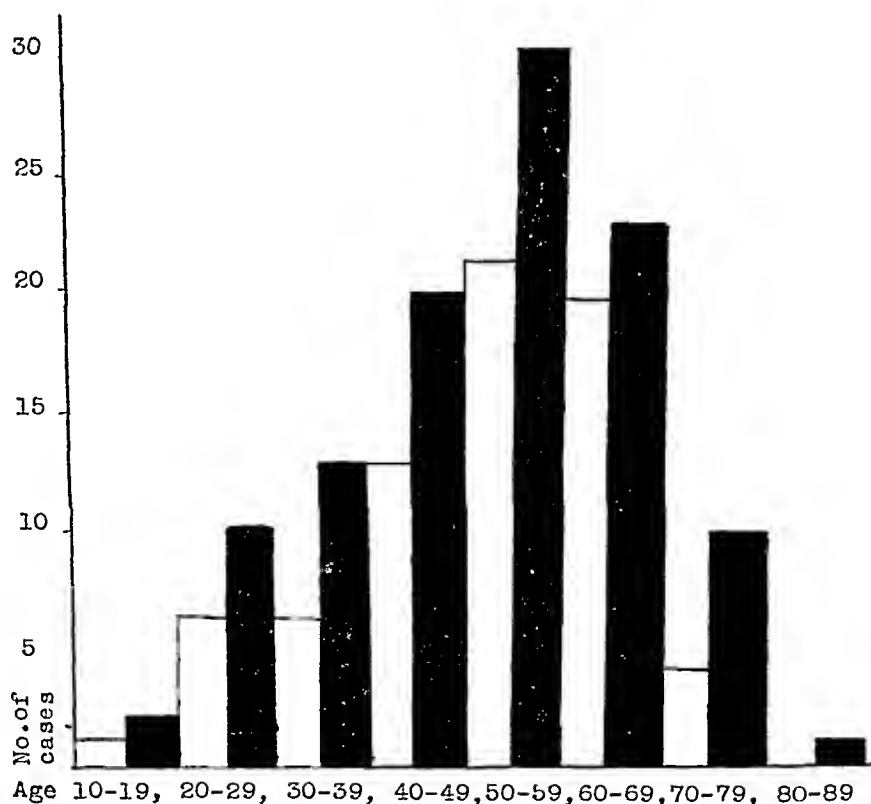


FIG 1 Number of cases of aortic stenosis in various decades ■ males, □ females

the sixth decade. The incidence in the fifth and seventh decades was considerable. The number of females in this series was considerably greater than that reported by Margolies² or Willius,⁴ but more closely approximated that given by McGinn and White.⁶ The preponderance of males may possibly be explained by the greater frequency of chorea as the rheumatic manifestation in the female sex and by the fact that chorea rarely is responsible for subsequent aortic involvement.

BLOOD PRESSURE CONSIDERATIONS

The average blood pressure of 147 cases of aortic stenosis, in which readings were available, was 145 mm of mercury systolic and 84 mm diastolic. The range varied from a highest systolic reading of 260 mm and a highest diastolic of 156 mm, to a lowest systolic of 80 mm and a lowest diastolic of 10 mm. That hypertension was common is shown by the fact that there were 17 with systolic readings over 200 mm and 22 with a diastolic over 110 mm. The average pressures for the 85 males was 138 mm systolic and 79 mm diastolic, that of the 62 females was 153 mm systolic and 81 mm diastolic (figures 2 and 3). This tendency for the females to have a higher blood pressure is in accord with findings obtained in a comparative study of the two sexes in relation to other forms of heart disease, such as mitral stenosis or angina pectoris.

There are two factors in addition to the stenosis of the aortic valve, which have some bearing on the blood pressure level. Insofar as there might be an accompanying aortic insufficiency there will be a tendency for the systolic pressure to be somewhat elevated and the diastolic to be depressed. Such effects are commonly observed in pure aortic insufficiency. The other factor is the one generally called essential hypertension, or that associated with an aging process. This will tend to show higher pressure readings in the older group. The common occurrence of hypertension in many types of cardiac disease makes one suspect that the intrinsic lesions of the heart may in some reflex fashion be partly responsible for hypertension. Another possibility is that the original etiological factor, namely rheumatic infection, may not only have been the cause of the valvular lesion but also may have produced changes in the peripheral vessels which eventually led to hypertension. The study of individual cases of aortic stenosis gives one the impression that when no other mechanisms are involved the systolic pressure is likely to be low and the diastolic slightly elevated, resulting in a small pulse pressure. Notwithstanding this, all ranges of systolic and diastolic levels from very low to very high may occur.

PHYSICAL FINDINGS

Among the physical findings in cases of aortic stenosis there are some that are more peculiarly diagnostic of the anatomical lesion, and there are others less characteristic because of their common occurrence in a variety of other conditions. A systolic thrill in the aortic area, roentgen-ray evi-

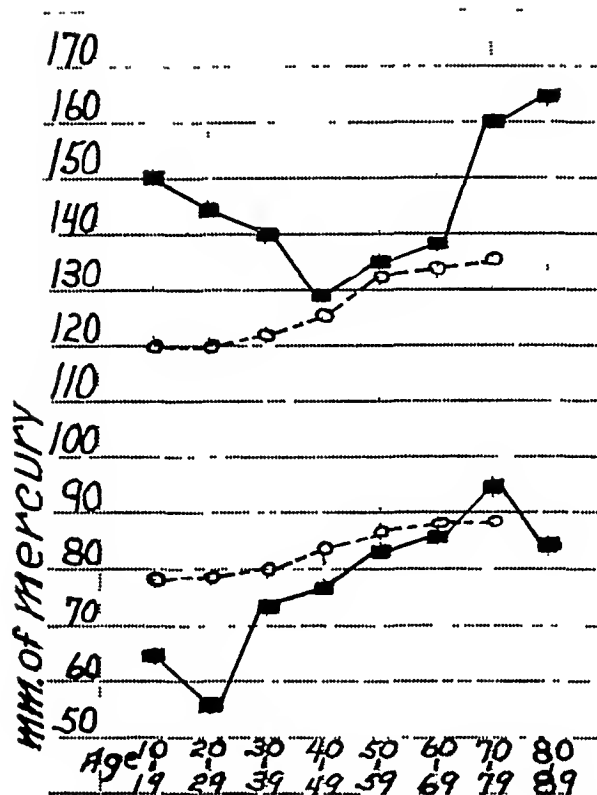


FIG 2 Average blood pressure readings of cases of aortic stenosis (solid squares), as compared to normal individuals (circles) Male group

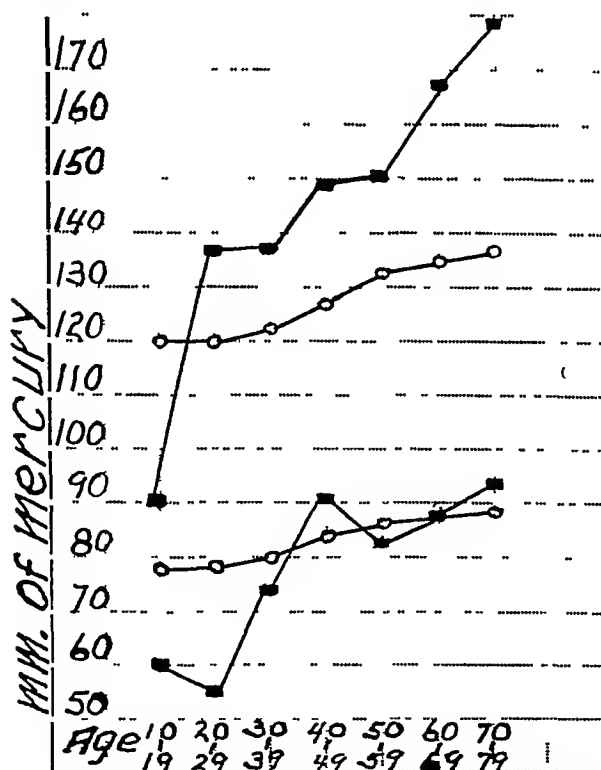


FIG 3 Average blood pressure readings of cases of aortic stenosis (solid squares), as compared to normal individuals (circles) Female group

dence of calcification of the aortic valve, a loud systolic murmur at the aortic area and a plateau pulse belong to the former group. Cardiac enlargement and an apical systolic murmur belong to the latter.

Cardiac hypertrophy is practically invariable in well marked aortic stenosis. In most cases this can be readily made out on physical examination, although during the early stages the percussion outlines do not always extend very much beyond normal limits. Marked dilation of the chambers such as occurs in mitral stenosis is not present as a rule, and therefore the cardiac silhouette is likely to be smaller, although the heart weight is greater in aortic stenosis than in mitral stenosis. In a previous study⁹ it was found that the average weight of the heart in cases of aortic stenosis was 669 grams while in cases of mitral stenosis it was 474 grams. The great difference is due to the marked hypertrophy of the left ventricle of the former. When the left border of dullness does not extend much beyond the nipple line the finding of a forceful apical impulse will often indicate that there is considerable hypertrophy of the left ventricle. This type of impulse, which lifts the finger slowly and remains lifted for an instant before it recedes, is quite unlike the short snapping impulse that is found in mitral stenosis.

An apical systolic murmur is a quite common finding but one that is difficult to appraise. It can be partly due to a transmission of a loud basal bruit, and to some extent it may result from an accompanying mitral insufficiency, either relative or structural in nature. Its presence or absence does not aid in establishing or eliminating the diagnosis of aortic stenosis.

The most constant physical finding is a loud basal systolic murmur best heard at the second right interspace, or over the midsternum. This murmur is often harsh in quality but we feel that its intensity is of greater importance than its quality. In fact one may say that faint murmurs are rarely harsh. When the loudness of murmurs was graded from I to VI¹⁰ as was done in many of the cases studied here, with rare exceptions the basal bruit was found to be of grade III intensity or louder. Often the apical murmur was just as loud as the basal and occasionally it was louder. There are other conditions in which loud systolic murmurs are heard at the base of the heart such as hypertension, congenital heart disease, anemia and hyperthyroidism. If these can be eliminated from consideration a loud aortic systolic murmur must always bring up the possibility of aortic stenosis. The direction of propagation of this murmur has been of no great aid in diagnosis. When loud it often could be heard throughout the chest, even in the right axilla. The importance of its transmission to the vessels of the neck has been exaggerated for this is due mainly to its intensity and to the proximity of its point of origin. There are occasional instances when the state of the circulation is so feeble that the murmur is quite faint and may only regain its loud and more characteristic intensity when the heart improves. It is in such cases particularly that roentgen-ray examination may be very valuable.

A blowing diastolic murmur heard in the second right interspace or along the left sternal border is a common, but by no means invariable finding in aortic stenosis. Stenosis of either the aortic or mitral valve frequently occurs without any auscultatory evidence of regurgitation. There are many instances of well marked mitral stenosis that show no systolic murmur whatever, and likewise many cases of aortic stenosis that have no diastolic murmur. In fact, of these 180 cases there were 87 in which no diastolic murmur was heard. To be sure this group excluded all cases with free aortic insufficiency, for this study was confined to well marked stenosis of the valve. In trying to elicit the aortic diastolic murmur, the fainter ones may be overlooked unless auscultation is carried out carefully, both in the recumbent and upright positions and during held expiration.

The most diagnostic physical finding is a systolic thrill. This is generally best felt at the aortic area but is occasionally present over the upper or midsternum and rarely to the left of the manubrium. A systolic impact must not be confused with a true thrill that has duration, for when the latter is really felt and congenital heart disease can be ruled out a diagnosis of aortic stenosis is almost certain. There will be very rare exceptions when a loud basal systolic murmur and a definite systolic thrill will be found and yet stenosis will be absent. The explanation of such findings is still obscure. The difficulty is that in less than one half of the cases will a thrill be palpable.

In only 21 of the 51 instances in this series that came to autopsy was a thrill found. Possibly in some, more careful palpation might have been more successful. In others terminal cardiac weakness may have been the cause of the absence of this sign. The thrill is often overlooked because palpation is not carried out or because when a thrill is faint it may be detectable only in certain positions. It may be necessary to have the patient sit up or lean forward or even hold a deep expiration while the base of the heart is palpated.

No careful analysis was made of the frequency of an absent aortic second sound, or the reliability of this sign in the diagnosis of aortic stenosis. We are certain, however, that in some of the cases a clear second sound was heard in the second right interspace, although in many it was either diminished or absent. In according importance to the character of the second sounds at the base one should remember that the sound heard over the aortic or the pulmonary area is not necessarily made by the corresponding valve. In some obvious cases of hypertension the second sound is louder over the pulmonary than over the aortic area, although aortic pressure is considerably higher than pulmonary pressure. Likewise in some cases of aortic stenosis a second sound heard to the right of the manubrium may be partly a transmission from the pulmonary snap. In general it may therefore be said that the aortic second sound in these cases occasionally is present, though generally diminished or absent.

A plateau form of peripheral pulse has long been regarded as a characteristic of aortic stenosis. The frequency with which this peculiarity of the pulse is observed is diminished by the difficulty of its recognition and also by the fact that its typical form is commonly altered in the presence of an accompanying aortic insufficiency or hypertension. However, there are instances in which careful attention to the quality of the radial pulse may supply valuable supportive evidence.

A peculiarity of the pulse less generally appreciated is that the rate not infrequently is slow. This was quite well known to the clinicians of former times for Fotheigill¹¹ in discussing aortic obstruction states, "the pulse is usually slow and steady." There are very few conditions apart from aortic stenosis in which the rate of the heart may be so slow in the presence of severe congestive heart failure, and where the slowing cannot be accounted for by a digitalis effect or heart block. This peculiarity on several occasions has been the first clue in reaching the correct diagnosis. The rhythm of the heart, unlike that observed in mitral stenosis, is generally regular. Of the 180 instances in this study auricular fibrillation was present in only 11 cases. Four of these were examined post mortem and none showed mitral stenosis. Factors such as age, sex, blood pressure and previous rheumatic infection were no different in the fibrillators than in those with regular rhythm.

ELECTROCARDIOGRAPHIC OBSERVATIONS

In 82 cases electrocardiographic studies were made. Our findings concerning conduction disturbances were similar to those recently reported.⁷ There were 14 instances of defective intraventricular conduction, including seven with typical bundle branch block. Three of the above 14 showed appreciable delay in the P-R interval and one had complete heart block. There were two additional cases of complete heart block. Conduction defects seemed to be more common in the cases of aortic stenosis that had angina pectoris than in those that did not have this complication. Eleven of the 82 cases had auricular fibrillation. Some of the others had extrasystoles of ventricular or nodal origin. It is significant that we did not have a single instance of right axis deviation in the entire series. If such a change in the electrical axis is found in aortic stenosis it should lead one to suspect an additional mitral stenosis. The main conclusion from the electrocardiographic studies is that defects in conduction are commonly associated with aortic stenosis.

ROENTGEN-RAY FINDINGS AND CALCIFICATION OF THE AORTIC VALVE

In the past there have been no distinctive roentgen-ray findings that characterized aortic stenosis. The boot shaped heart denoting a hypertrophied left ventricle, although common in aortic stenosis is also frequently present in pure aortic insufficiency and in some cases of hypertensive heart disease with left ventricular hypertrophy. Recently, however, the detection

of calcification in the aortic valve by fluoroscopic examination¹² has been of tremendous diagnostic value. This has invariably been indicative of a significant degree of stenosis of the valve. Inasmuch as this technic has been developed in the past several years, only 32 of the more recent cases of this series were fluoroscoped. Among these there were 26 instances in which this examination positively identified calcification of the aortic valve. Two of the remaining six were examined post mortem, one showed calcification, the other did not. It is evident that aortic stenosis may be present for a long period of time before calcification occurs in the leaflets. Such cases will necessarily be negative on fluoroscopy, and others may be missed because of the thickness of the chest wall or the faintness of the shadow. It also follows that calcification will be found more readily in the long standing cases. This is well borne out by the following figures. The average age of the group showing calcification was 60.3 years while that of the negative group was 42.6 years. The youngest of the positive cases was 45 years old, although younger individuals not included in this study have shown calcification of the valves by roentgen-ray. The value of roentgenographic examination is readily appreciated by the fact that in one half of the 26 cases, no aortic systolic thrill could be felt. In some of these the roentgen-ray was the only means of establishing the diagnosis. At present it may be stated that the roentgenological finding of calcification of the aortic valve is the most accurate single evidence of aortic stenosis, but that calcification may not be detectable during the early years of the production of this lesion.

THE OCCURRENCE OF ANGINA PECTORIS

Little mention was made in the older writings concerning the association of angina pectoris with aortic stenosis. Mackenzie¹³ stated that, "there may be symptoms of angina pectoris but these are due to associated changes in the heart muscle." Recently more attention has been paid to this relationship^{6, 7, 14}. The more recent teaching has been that although angina pectoris is commonly associated with aortic valvular disease it is due to insufficiency of the valve rather than to stenosis. The explanation that is offered for this association is that coronary flow takes place during diastole and that with the low diastolic pressure that accompanies aortic insufficiency there is inadequate flow through the coronary system with resultant relative myocardial anoxemia. This explanation is open to some doubt for there are those who believe that the main flow through the heart occurs during systole¹⁵. Apart from the theoretical controversy there are certain clinical experiences which make one doubt the accepted importance of aortic regurgitation in the production of anginal pain.

Free aortic insufficiency, syphilitic in origin, is rarely associated with angina except in those cases in which the coronary orifices are narrowed. Furthermore, as will be seen from the following data, angina occurs quite

commonly in aortic stenosis without any clinical evidence of insufficiency of the valve. The following explanation was kindly suggested to us by Dr Tinsley R. Harrison: "The two important points about angina and aortic stenosis seem to be (1) that there is no evidence of anything which can decrease the circulation to the heart in these cases and (2) that in such patients there is much less relationship of the pain to exercise than in ordinary coronary angina. As regards the first point, while in cases without aortic stenosis one almost always finds at autopsy either coronary arteriosclerosis, luetic narrowing of a coronary orifice, or a well marked aortic insufficiency with a low diastolic pressure during life (the latter producing angina by causing interference with the blood supply to the heart during diastole), in persons with aortic stenosis typical anginal seizures may occur in the absence of any of these factors, the aortic insufficiency either not being present at all or in many cases of such mild degree as to cause no lowering of the diastolic pressure. In such cases the pathological evidence does not point toward a diminution in coronary flow and the enlarged coronary arteries suggest that the flow during life was actually greater than normal. However, this does not mean that the mechanism of angina is any different in such cases from that occurring in other patients. The coronary flow has to be looked at not per se but from the standpoint of its relationship to the need for blood, the latter of course depends on the oxygen consumption of the heart, which in turn depends largely on the work done by the heart. The latter depends on three factors—the amount of blood expelled per unit of time, the pressure against which this blood is expelled, and the energy expended in imparting velocity to this blood. As regards the output of blood, the only case which we studied had a normal cardiac output. However, the pressure within the ventricle during systole is probably enormously increased and this of course tends to increase the cardiac work. Furthermore, while the velocity factor is, under certain conditions, a relatively small fraction of the cardiac work, it may become the greatest factor in aortic stenosis, where with a markedly narrowed orifice the rate of flow must be enormously greater during systole. It is possible and indeed quite likely that the velocity factor is more than 50 per cent of the cardiac work in a case of marked aortic stenosis. Therefore, even though the coronary flow increases, say three-fold, it is quite likely that the cardiac work may be increased four-fold, and this would of course tend to produce angina through the usual mechanism of myocardial anoxemia.

"As regards the second point, in the young patients with aortic stenosis we do not have pipe-stem coronaries but normal vessels which are capable of opening and closing. The attacks which come on at rest may very well be due to slight vasomotor changes in the caliber of the coronaries. Suppose that the arteries are wide open and are just able to transmit enough blood to prevent angina. Then even a very slight diminution in caliber could cause an attack. This is quite different from a normal person, where the arteries have large reserve and different from a person with extensive

coronary sclerosis where one can't imagine any opening and closing of the pipe-stem vessels "

Another explanation depends on the likeness of the aorta and coronary system to the common water faucet suction pump. The water flowing through the larger orifice causes a suction on the smaller orifice which enters it at right angles. The amount of suction is somewhat dependent upon the velocity of flow through the larger orifice. It seems reasonable to assume that in the normal heart with "paper thin" aortic valves, during systole these leaflets are fairly close to the coronary ostia preventing any such suction action. In cases of aortic stenosis with rigid, calcified immovable aortic valves, and markedly increased velocity of the blood flow, it is possible that this suction action may even draw blood out of the coronary arteries and lead to relative myocardial ischemia.

It was significant but by no means surprising that as many as 41 of the 180 cases, or 22.7 per cent had definite angina pectoris. (There were 28 additional questionable cases.) Of these 41 cases 22 were male and 19 were female, the average age of the former was 49 years (youngest 13 and oldest 64) and of the latter 59 years (youngest 25 and oldest 74). There was one case in the second decade, two in the third, three in the fourth, seven in the fifth, and the remaining 28 in the later decades. The average blood pressures for the two sexes in these cases were 136 mm systolic and 80 mm diastolic in the males, and 154 mm systolic and 85 mm diastolic in the females. These figures were similar to the blood pressure readings of the cases of aortic stenosis in general, but somewhat lower than those found in angina pectoris, unassociated with aortic stenosis.¹⁶ It follows that hypertension is not a factor in the causation of angina associated with aortic stenosis.

The frequent absence of aortic insufficiency in this group with angina pectoris is indicated by the fact that in 19 of the 41 instances, no diastolic murmur was heard. This signifies that not only is pure aortic stenosis a common occurrence but that a concomitant angina is frequently present without an accompanying regurgitation.

To further validate this point of view 31 consecutive cases of free aortic insufficiency were studied. Only four were found to have angina pectoris and they were all luetic. Very likely the coronary orifices were involved in these. The average age of the 31 cases was 41.6 years and nine of them were over 50 years of age. The blood pressure readings in this group were typical of free aortic insufficiency, the average readings being systolic 154 mm and diastolic 32 mm. In 15 instances a definite past history of rheumatic fever was obtained but the lesion had not progressed to detectable clinical aortic stenosis. The comparative rarity of angina in these cases of aortic insufficiency is in striking contrast to its frequency when the aortic valve is stenosed.

Inasmuch as the diagnosis of angina pectoris can only be made by a proper appraisal of the symptoms and because the subjective complaints that

lead to this diagnosis are often mild and may be over-shadowed by the more distressing breathlessness, the diagnosis is often overlooked. In many cases one has to initiate a direct inquiry into the possibility of any ill feeling in the chest on hurrying in the street, because the patient often will not spontaneously mention it. We feel that this type of careful questioning was responsible for the large number of cases of angina detected in this study. The importance of eliciting these symptoms lies in the fact that the frequency of angina throws some light on the prevalence of sudden unexpected death in aortic stenosis. Whenever the diagnosis of angina pectoris is correctly made one infers that that patient is subject to such a fatal outcome. It is interesting that of the 80 cases in which the type of death was known, nine dropped dead suddenly. In five of these nine cases a diagnosis of angina pectoris had already been made. We believe that in some of the others that died suddenly a diagnosis of angina pectoris could have been made if we had had the opportunity of inquiring carefully into the history.

One experience that we had bears directly on this point. A man of 50 entered the hospital complaining of increasing breathlessness. He showed the typical signs of aortic stenosis and marked congestive failure, and was studied most carefully by many physicians including ourselves. He improved on medical treatment and returned about one year later with recurrent failure. On this second admission a clear cut history was elicited by direct questioning of anginal distress, that antedated the first admission. It had been entirely overlooked by all members of the staff. After he had again recovered a fair degree of compensation and while feeling quite comfortable, he died instantly. If a proper history had not by chance been obtained he would have been classified in that vague group of cases of sudden death from aortic stenosis. Sudden death of this type can occur even in the very young who have aortic stenosis and angina pectoris, as was the case in a boy of 15 in whom both of these diagnoses were made, who dropped dead while going to school.

The duration of life in cases of aortic stenosis after the development of angina pectoris is not very different from what is found in ordinary angina. In the 19 patients of this present series who were known to have died, the duration of life after anginal pain first occurred was 3.3 years. Of 10 who were known to be still alive the duration was 5.5 years. The cases varied considerably and were too few in number to permit drawing any clear cut conclusions, but we have the general impression that the young rheumatic aortic case with anginal pain may carry on many years, although typical sudden fatality may occur at any time.

SYNCOPE

The occurrence of syncope in aortic stenosis was lost sight of until a few years ago. This was recently discussed by McGinn and White⁶ and in greater detail by Marvin and Sullivan¹. Knowledge of the rôle that the

carotid sinus may play in the production of syncope,¹⁷ naturally led to the suspicion that this same mechanism might account for the dizziness and fainting attacks that occur in aortic stenosis. With this in mind an investigation was carried out to test the irritability of the carotid sinus in some of these cases. In 19 a test for carotid sinus irritability was performed on each side and in none were positive results obtained for syncope, or dizziness was not produced*. Among these were two with a clear cut history of syncopal attacks. From this it seems unlikely that carotid sinus irritability can be a common occurrence in aortic stenosis or that it will explain, in the majority of cases, either the dizziness and fainting, or the sudden death. The possible rôle of the carotid sinus cannot be dismissed entirely, however, and further investigation is necessary. It is possible that reflex inhibition of the heart from a sensitive carotid sinus may be the cause of sudden death in rare instances. A more likely cause of sudden death is the same mechanism that prevails in ordinary angina. This assumption is particularly applicable in those cases in which the diagnosis of angina pectoris can be made. One may even postulate that some of the others die suddenly in their first attack of angina.

An attempt was made to detect clinical features which were characteristic of cases showing syncope or dizziness. There were 21 instances of true syncope and an additional 16 had significant dizziness without syncope. The average age of those with true syncope was five years greater among the males and 10 years greater among the females than the general averages. Despite their more advanced years those with syncope tended to have a somewhat lower blood pressure. Although these two differences were not great they may have some bearing on the production of the cerebral symptoms since both age and lower blood pressure may predispose to cerebral anoxemia.

TYPE OF DEATH

Ninety-five of 180 cases studied were known to have died. Of these 18 died of unknown cause, 44 died of congestive heart failure, 15 of subacute bacterial endocarditis, four of coronary thrombosis, two of cerebral accidents, two of pneumonia and one of Adams-Stokes disease. The remaining nine died suddenly and unexpectedly. There were some differences in age between these various groups. Although the average age at death of all the fatal cases was 51.3 years, the group with subacute bacterial endocarditis died at an average age of 36 years. Those that died suddenly had an average age of 45 years. The three most common types of death are congestive failure, subacute bacterial endocarditis and angina pectoris.

It is of some interest to analyze the duration of the more important subjective symptoms and objective findings in the group of fatal cases. Such an analysis gives one a guide as to the prognosis when particular

* Since this study was completed two cases of aortic stenosis were seen without any previous history of syncope or dizziness that showed definite positive reactions to carotid sinus stimulation.

features develop in the progress of the disease. Palpitation of the heart was an early complaint and the average duration of life after its onset was eight years. Dyspnea on the other hand came much later, as the average length of life after its first occurrence was only 23 months. The average period of survival after edema was 9.3 months and after appearance of syncope 9.1 months. Syncopal attacks that occurred early in life, 15 years or so before the patient was seen, were disregarded as they were considered to be unrelated to the disease. The duration of life after congestive râles were found in the lungs and definite pitting edema of the legs occurred was 6.3 and 4.3 months, respectively. In many of these cases the features just enumerated may have been present for some time before they were first noted, but in general it may be said that life expectancy is quite short once clear cut heart failure has developed.

DIAGNOSTIC CONSIDERATIONS

The more important diagnostic findings in aortic stenosis are a loud systolic murmur at the base of the heart, a basal systolic thrill, a plateau pulse and calcification of the aortic valve on fluoroscopic examination. The presence of a true thrill or calcification by roentgen-ray are quite reliable diagnostically. The other two features are not as trustworthy. This explains the difficulty in diagnosis and the fact that the majority of cases are overlooked. It is obvious that a fair degree of stenosis must exist for years before all the above criteria will be apparent. The early stages of the process must therefore be diagnosed on data that have been regarded in the past as inadequate. In a previous publication¹⁰ attention has been called to the importance of interpreting the presence of a systolic murmur as a possible early sign of aortic stenosis. In fact it was found that during the early stages a moderately loud systolic murmur that eventually proves to be due to aortic stenosis could be somewhat louder at the apex of the heart or the mid-precordium than in the aortic area. Also some cases regarded as having benign or insignificant systolic murmurs eventually prove to have aortic stenosis. With this in mind an analysis was made of 16 cases seen by one of us over the course of years, that eventually proved to have definite aortic stenosis but that had previously been misdiagnosed. Four of these were thought to have had mitral insufficiency, four aortic insufficiency, one a normal heart with a benign systolic murmur, six hypertensive heart disease and one chronic myocarditis. In none of these was a systolic thrill present at first, but in all either a systolic thrill or calcification of aortic valve or both developed. In conclusion it may be emphasized that loud basal systolic murmurs, especially in the absence of hypertension, must lead one to suspect the presence of aortic stenosis and make one search all the more diligently for other more convincing evidence.

POSTMORTEM FINDINGS

The main pathological finding that was investigated in this group of cases was the condition of the coronary arteries. The question naturally arises whether angina pectoris which accompanies aortic stenosis is due to atheromatous changes in the coronary arteries similar to those seen in patients without aortic stenosis or to the valvular lesion itself. The frequent occurrence of pathological changes in the coronary system in older people makes it necessary to appraise this problem in the younger group.

There were nine cases in this study with angina pectoris that were examined post mortem. Six were over and three were under 50 years of age. Two of the older group, aged 71 and 66, merely showed minimal changes in the coronary arteries without any narrowing of the vessels or infarction of the heart muscle. One case, aged 52, showed moderate sclerosis with narrowing of the coronary arteries and no myocardial infarction. Another, aged 66, had marked sclerosis and narrowing of the vessels with several small old infarctions. There was one, aged 62, that showed typical coronary thrombosis with infarction of the ventricle. The last one of this group, aged 52, had syphilitic aortitis, almost completely occluding both coronary orifices. Two of the younger cases, aged 46 and 25, had perfectly normal coronary arteries and the third, aged 46, showed moderate coronary changes without narrowing of the vessels. None of the last three had any old or recent infarctions of the ventricle. The complete absence of any alterations in the coronary system in two of the younger cases and the occurrence of only minimal alteration in some of the others, we consider as adequate proof that the anginal attacks were due to some other cause. It is more logical to regard this other factor as the actual valvular lesion. How this burden may be conducive to anginal attacks has previously been discussed.

Another pathological finding of interest is the localization of the calcification to the aortic valve and the ring. The deposits did not extend up to the mouth of the coronary vessels, which were distinctly free and open. In fact many cases of aortic stenosis, even in the older group, were comparatively free of atheromatous changes in the wall of the aorta itself.

SUMMARY

- 1 A study was made of 180 cases of aortic stenosis, unassociated with any other significant valve disease, 53 of which were examined post mortem.
- 2 Evidence was presented to indicate that the etiology in most instances was a previous rheumatic infection. It was thought that some early ill defined infections may have been the cause in a few cases.
- 3 It was found that although the male sex predominates, the ratio was not more than three to two. The largest number occurred in the sixth decade.
- 4 The average blood pressure of the males was 138 mm of mercury systolic and 79 mm diastolic, and for the females 153 mm systolic and

81 mm diastolic The range of these readings, however, varied from very low to very high systolic and diastolic levels

5 The most distinctive physical findings in aortic stenosis were a loud basal systolic murmur, a systolic thrill near the aortic area, and the detection of calcification of the valve on fluoroscopic examination In about one half of the cases no aortic diastolic murmur was audible

6 Disturbances in conduction such as bundle branch block and auriculo ventricular block were quite common

7 Twenty-six of 32 cases that were examined showed calcification of the valve fluoroscopically

8 Angina pectoris was found to be quite common, occurring in 22.7 per cent of the cases There is reason to believe that many cases are overlooked because of inadequate histories An explanation of the possible mechanism of angina in these cases, not dependent upon coronary sclerosis was suggested

9 There were 21 instances of syncope in this series In four of these and 15 other cases the sensitivity of the carotid sinus was tested and found normal It was found that sudden death occurred particularly in those with an anginal history, and that the carotid sinus was an unlikely cause of such eventuality

10 The three most common types of death were congestive heart failure, subacute bacterial endocarditis, and sudden death Once major symptoms developed in this group the average life expectancy was short

11 Although the finding of a basal systolic thrill or calcification on roentgen-ray examination are very reliable evidences of aortic stenosis, the diagnosis in many cases and especially during the early stages, will have to depend upon the intelligent appraisal of a moderately loud basal systolic murmur

12 A study of the postmortem material showed that the calcification is limited to the valve and does not involve the coronary orifices The finding of normal coronary vessels in two of the young patients who had angina, and the presence of only minimal atheroma in the vessels of some of the others that had angina strongly suggest that the deformity of the valve itself is in some way responsible for this complication

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CHLOROSIS ¹

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CHLOROSIS is defined by Patek and Heath ¹ as "a hypochromic anemia in adolescent girls and young women, usually associated with gastrointestinal and menstrual disorders." According to many observers, Naegeli ² and Witts ³ among others, this condition, previously common, has become a disease largely of historical interest. Many of the younger clinicians who have not seen typical cases of classical adolescent chlorosis are inclined to doubt altogether the existence of this type of anemia. There is no doubt that chlorosis was quite frequent a quarter of a century ago. Its high incidence then, however, was more apparent than real. This is obvious from von Hoesslin's ⁴ critical analysis of 143 cases diagnosed as chlorosis. Of these 64 had histories suggesting tuberculosis, 25, gastric ulcer, 13, psychoneurosis, 13, secondary anemia due to endocarditis or other infections, and 5, excessive blood loss. The remaining 23 cases might have been called "possible chlorosis."

There are three factors responsible for the remarkable decrease in the frequency of this disease. The first is the introduction of more accurate diagnostic methods in the beginning of the twentieth century: the improvement in the chemical tests for occult blood in stools by Weber ⁵ who introduced the guaiac test, and by the Adles ⁶ who introduced the benzidine test, the discovery of the roentgen-ray by Conrad Roentgen in 1895, the introduction of accurate methods for hemoglobin determination by Gowers, ⁷ Veillon, ⁸ Tallquist, ⁹ Dare, ¹⁰ Haldane ¹¹ and Sahli ¹². Thus many cases previously diagnosed as chlorosis were discovered to have tuberculosis or some bleeding lesion in the gastrointestinal tract. A number of apparently pale patients were found to have normal hemoglobin values. The second factor is the improvement in the general and personal hygiene of the population. The third is the placing of many mild and some severe cases of chlorosis in the categories of nutritional anemias or microcytic anemia with achlorhydria.

Three cases of apparently classical adolescent chlorosis were seen by me recently. In view of the supposed rarity of this type of anemia the cases are presented here somewhat in detail.

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CASL RLPORTS

Case 1 A girl, aged 19, was first seen in November 1936, complaining of weakness, some shortness of breath, palpitation and vague pains in the lower abdomen. She was born in Scotland and came to the United States at the age of two years. She was born at term and was of normal weight at birth. She received neither orange juice nor cod liver oil during early infancy. Her appetite has always been capricious and her diet grossly deficient in green vegetables and meats. At the age of five years she was told she was anemic and was given some medicine for the anemia, this she took for a short time. At the age of 10 years she was told again by a physician that she was anemic, this time she took the prescribed medicine for about one month. Her menses began at the age of 14 years, have always been very scanty, particularly during the past year.

There was no history of any previous serious illnesses or operations.

On examination the patient appeared well developed and plump. She had a temperature of 100° F (37.8° C) by mouth. The skin was strikingly white. The face was definitely puffy. The sclerae were not icteric. The mucous membranes of the mouth were very pale. The tongue appeared normal. The heart was normal except for a soft systolic murmur over the mitral area. Examination of the lungs, abdomen, pelvis and rectum was negative. The extremities were negative except for some pretibial pitting edema. The finger nails appeared rather thin.

The urine and stools were normal. Analysis of the fasting gastric contents revealed complete absence of free hydrochloric acid. After histamine injection the free hydrochloric acid rose to 10 units. The blood Hinton reaction was negative. The other initial laboratory findings are presented in table 1.

TABLE I
Initial Laboratory Findings in the Three Cases of Chlorosis

Case	Red blood cells per cu mm	Hemoglobin, per cent (Sahli)	Mean corpuscular volume of red cells, cu microns	Average diameter of red cells, microns	White blood cells per cu mm	Differential leukocyte count, per cent				Platelets per cu mm	Plasma proteins, grams per cent			Icteric index
						Polymorphonuclears	Lymphocytes	Monocytes	Eosinophiles		Total proteins	Albumin	Globulin	
1	4,920,000	52	67.0	7.21	10,750	69	16	11	4	2,671,000	5.6	3.1	2.5	5
2	4,440,000	55	—	6.66	7,500	58	35	5	2	499,000	4.7	2.7	2.0	5
3	4,160,000	50	—	6.74	6,300	55	37	6	2	1,467,000	6.3	3.1	3.2	5

The stained blood films of all three cases revealed small, pale red cells showing moderate anisocytosis and poikilocytosis.

This patient improved fairly rapidly under iron medication. The duration and quantity of her menses became more normal. The subsequent changes in the various blood constituents are presented in chart 1.

Case 2 A girl, aged 19 years, was first seen by Dr Frank Mirabello in November 1936. She complained then of a mild "head cold." She was born in Nova Scotia and had been in the United States for three years. She was born at term and had normal weight at birth. Her diet has always been adequate. Her menstruation began at the age of 13 years, and the quantity, duration and recurrence of the menses have been apparently normal.

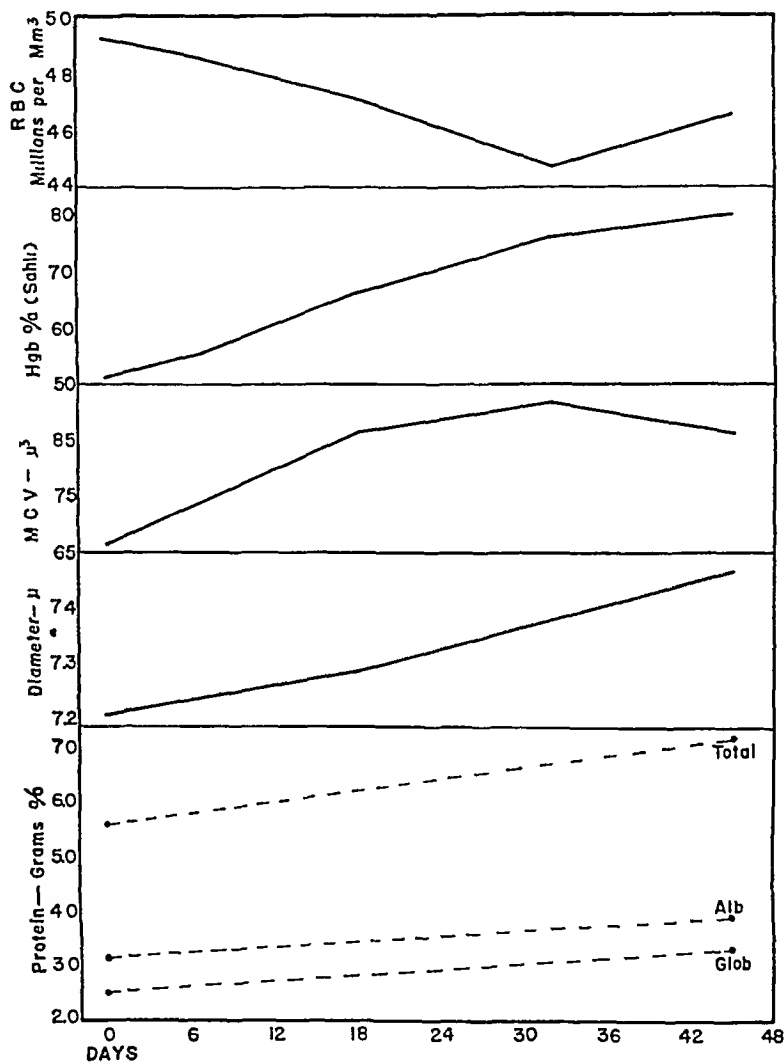


CHART 1 The behavior of the red blood cell count, hemoglobin, mean corpuscular volume of the erythrocytes, average red cell diameter and plasma proteins in case 1 under iron therapy

On examination the patient appeared well developed, but rather thin. There was slight swelling and reddening of the mucous membranes of the nose and some generalized injection of the throat. The temperature was normal. There was moderate pallor of the mucous membranes of the mouth. The tongue was normal. The heart, lungs, abdomen and extremities were negative. The finger nails were normal.

The urine and stools were negative. Gastric analysis revealed complete absence of free hydrochloric acid after a caffeine test meal. The blood Hinton test was negative. The remaining initial laboratory findings are given in table 1.

This patient improved rapidly with iron medication. At the end of five weeks the red blood cell count was 5.33 millions per cubic millimeter, hemoglobin 82 per cent (Sahli).

Case 3. This patient is a twin sister of case 2. The history she presented is identical with that given by her sister. She was seen first by Dr. Mirabello in November 1936, complaining then of a mild acute upper respiratory infection. On examination the patient appeared well developed and well nourished. There was slight swelling of the nasal mucous membrane and slight reddening of the throat. The temperature was normal. There was moderate pallor of the mucous membranes of the mouth. The tongue was normal. The heart, lungs, abdomen and extremities were negative. The finger nails were normal.

The urine and stools were negative. Gastric analysis revealed post-histamine achlorhydria. The blood Hinton reaction was negative. The remaining initial laboratory findings are presented in table 1.

This patient improved rapidly under treatment with iron. At the end of five weeks her red blood cell count was 5.4 millions per cubic millimeter and the hemoglobin 74 per cent (Sahli).

The most significant deviations from the normal in patients with chlorosis are to be found in (1) the gastric secretions, (2) the blood plasma proteins, (3) the red cells, and (4) the blood platelets.

Gastric Secretions. It is frequently stated that in chlorosis hyperacidity is common and achlorhydria rare. However, one of my patients revealed hypoacidity after the injection of histamine, another, achlorhydria after a caffeine test meal and the third, complete post-histamine achlorhydria. Of Patek and Heath's¹ four cases, one exhibited normal gastric secretion, two hypoacidity following histamine injection and one complete post-histamine achlorhydria. It would seem, therefore, that hypoacidity and even complete post-histamine achlorhydria are not rare in chlorosis.

Blood Plasma Proteins. It has been pointed out (Naegeli,² Brugsch¹³) that in this disease the total plasma proteins may be reduced with the albumin-globulin ratio remaining normal. Two of my patients showed a reduction in the total plasma proteins. Decrease in the plasma proteins has been noted, however, in other types of anemia and has been observed also by Wintrobe¹⁴ in primary hypochromic anemia. When the reduction in the plasma proteins is considerable, edema may appear. However, the production of edema is not dependent solely upon the actual level of the plasma proteins (critical level is 5.5 ± 0.3 per cent, according to Moore and Van Slyke¹⁵), although this constitutes the most significant single factor. There are other factors, such as the total fluid intake and sodium chloride intake, which may play important rôles. It is perhaps for this reason that case 1 with a total plasma protein of 5.6 grams per cent exhibited edema, while case 2 with a total plasma protein of 4.7 grams showed no edema whatever.

Red Cells. The total red cell count is frequently normal or even elevated above the normal level. The erythrocytes are small in size and poor in

hemoglobin and produce a hypochromic microcytic anemia of the type seen in conditions such as primary hypochromic anemia, nutritional anemia, chronic blood loss and hookworm disease (Wintrobe¹⁶), microcytic hypochromic anemia in infants and children (Faber et al¹⁷) and certain nutritional anemias in infants and children (Josephs¹⁸) The anatomy of the red cell in chlorosis is well illustrated by a diagram suggested by Haden¹⁹ showing a cross section view of the mean cell in various clinical conditions (figure 1)

Blood Platelets The most striking hematologic finding in patients with chlorosis is the frequently encountered thrombocytosis which may be very

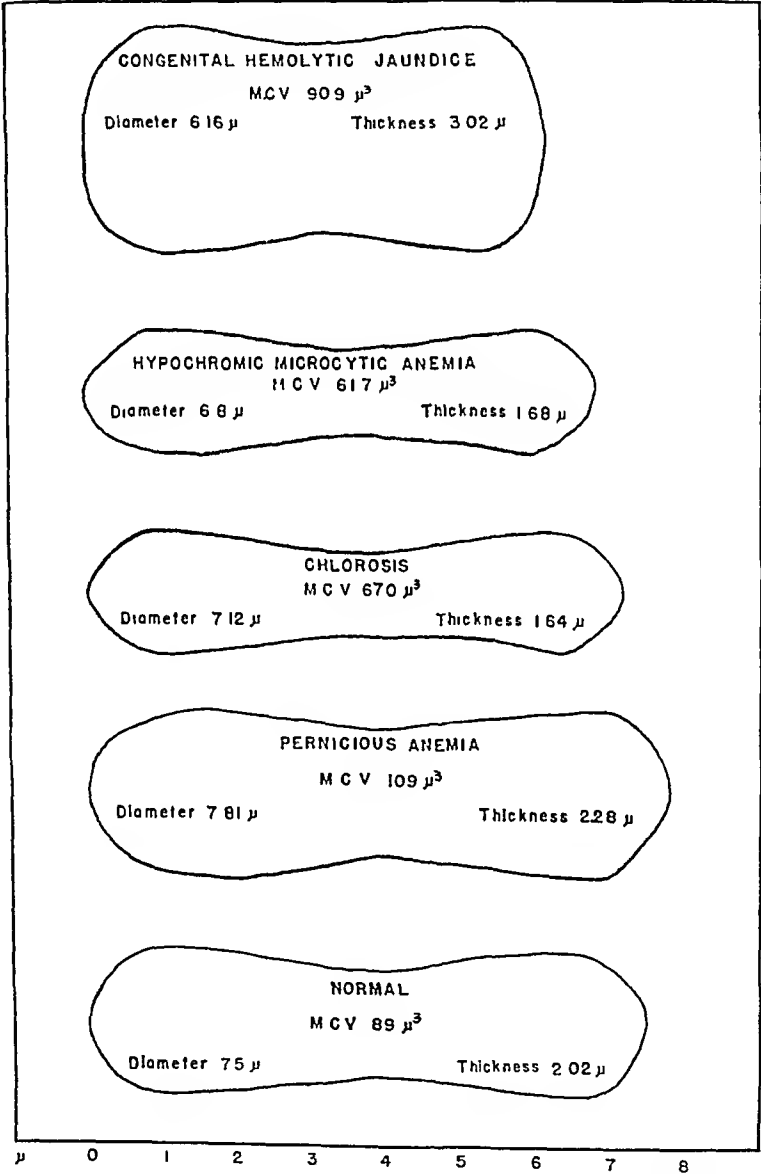


FIG 1 Cross section and measurements of the erythrocytes in various clinical conditions

marked (table 1, chart 2) According to the method described by me elsewhere²⁰ the platelets may be divided, according to size, into four groups Group I, consisting of small platelets the diameter of which is one-quarter that of a red cell, or about 1.8 microns, group II, consisting of medium-sized platelets with a diameter one-third that of a red cell, or about 2.5 microns, group III, consisting of large-sized platelets with a diameter one-half that of a red cell or greater, or about 3.6 microns, and group IV, consisting of irregularly shaped platelets The differential platelet formula of normal adults is usually as follows Group I, about 19 per cent, group II, about 63 per cent, group III, about 17 per cent, and group IV, about 1 per cent The small platelets, those belonging to group I, are the juvenile forms and have been shown by Baita²¹ Zeller²² Jurgens and Naumann²³ and Jurgens²⁴ to agglutinate very readily The thrombocytosis in patients with chlorosis is characterized by the presence of numerous small platelets of group I These juvenile, easily agglutinating platelets constitute a significant predisposing factor in the development of spontaneous venous thrombosis at times observed in this condition (in 2 to 3 per cent of cases, according to Cabot²⁵) Chlorosis must be classed, therefore, as a definite thrombophilia along with conditions such as certain post-splenectomy states (Rosenthal²⁶), postoperative states (Hueck²⁷), fractures of long bones (Galloway²⁸), parturition (Dawbarn, Earlam and Evans²⁹), tuberculosis (Brock and Rake³⁰), malignancy (Naegeli³¹), polycythemia vera (Jurgens and Bach³¹), severe acute hemorrhage (Jagic and Klima³²) and post-infectious states In all these conditions the tendency to the development of spontaneous venous thrombosis is always associated with an elevated platelet count Essential thrombophilia recently described by Nygaard and Brown³ seems to constitute an exception, for in this condition the platelet count is normal The behavior of the total and differential platelet counts in chlorosis under iron therapy is totally different from the behavior of the thrombocytes in other types of anemia during treatment (chart 2)

There has been considerable diversity of opinion regarding the possible relationship between classical adolescent chlorosis, summarized recently by Patek and Heath,¹ and primary hypochromic anemia (called also idiopathic hypochromic anemia, simple achlorhydric anemia, cryptogenic achylic chloranemia, chronic chlorosis, hypochromic gastrogenous anemia) first clearly defined by Faber³⁴ and described more recently in detail by Witts,⁵ Dameshek,³⁶ Minot³⁷ and Wintrobe and Beebe³⁸ Thus Witts³ is of the opinion that, in the absence of achlorhydria and dysphagia, the microcytic hypochromic anemia in middle-aged women is allied to adolescent chlorosis Bloomfield³⁹ maintains that it is impossible to differentiate chlorosis from primary hypochromic anemia It seems to me, however, that chlorosis is a definite disease entity a view entertained by many observers, Minot³⁷ among others It occurs in two forms, a severe one which is rather infrequent and a mild one which is, according to Davidson,⁴⁰ quite common It presents a number of characteristic features differentiating it definitely from

primary hypochromic anemia, as shown in table 2. It must be admitted that atypical cases of both conditions are occasionally encountered which seem indistinguishable.

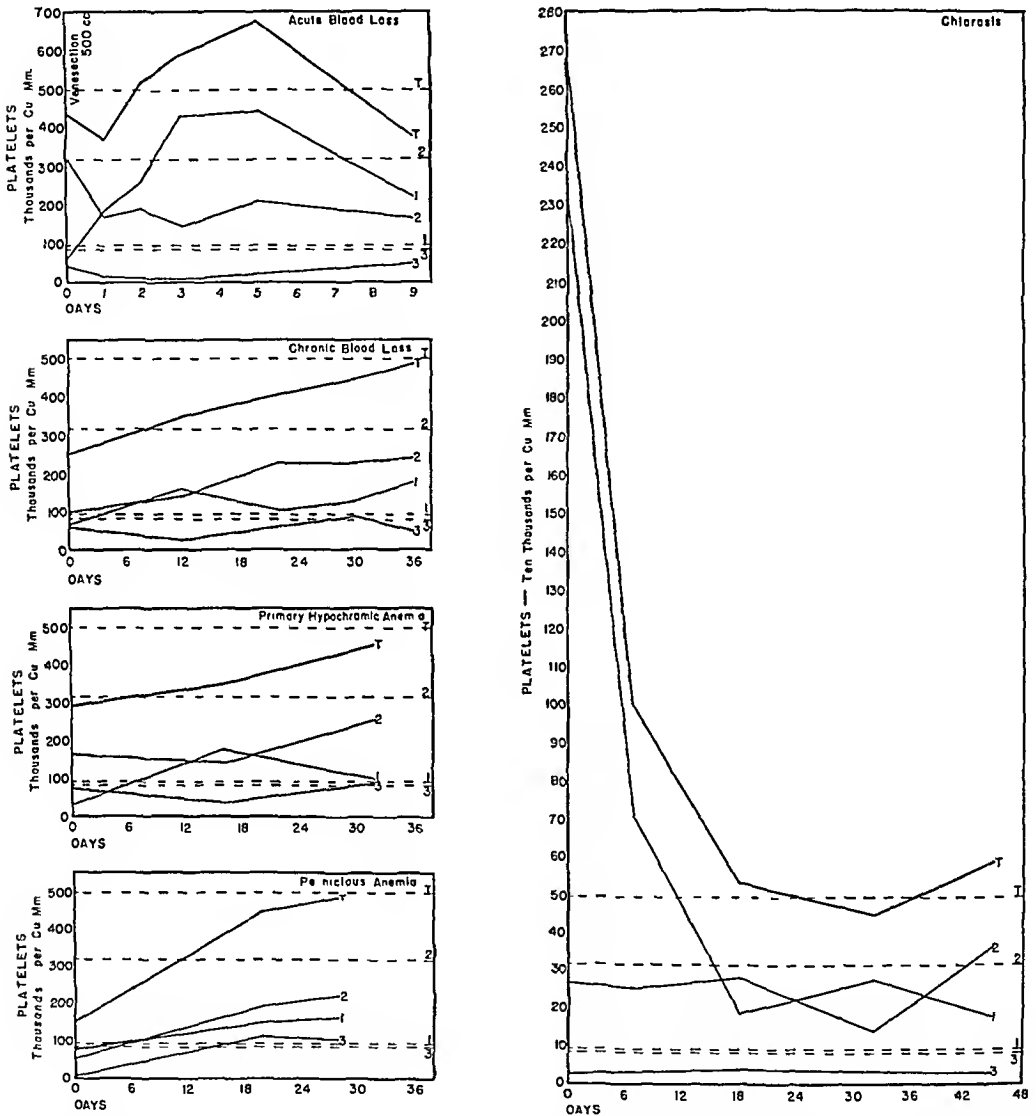


CHART 2 The behavior of the total and differential platelet counts in acute blood loss (venesection of 500 cc of blood on a normal adult who acted as donor for blood transfusion), chronic blood loss (chronic bleeding peptic ulcer), primary hypochromic anemia under iron therapy, pernicious anemia under liver therapy and chlorosis (case 1) under iron therapy. Dotted lines T represent the normal platelet levels, and dotted lines 1, 2 and 3, the normal absolute levels of the corresponding groups. Continuous lines T represent the behavior of the total platelet counts, and continuous lines 1, 2 and 3, that of the absolute counts of the corresponding groups.

SUMMARY AND CONCLUSIONS

Chlorosis, common a quarter of a century ago, has not disappeared. It is a definite clinical entity possessing characteristic features differing in

TABLE II
Differential Features Between Chlorosis and Primary Hypochromic Anemia

	Chlorosis	Primary Hypochromic Anemia
<i>Age</i>	14 to 20 years	Usually fourth decade
<i>Sex</i>	Limited to females	Usually in females, occurs rarely in males
<i>Symptoms</i>	Those of anemia	In addition to those of anemia, frequently sore tongue, dysphagia (Plummer-Vinson syndrome), paresthesias, diarrhea
<i>Skin</i>	Normal in appearance and texture, amount of pigmentation may be very scanty	Often dry, inelastic, may present abnormal pigmentation
<i>Hair</i>	Normal	Frequently dry, prematurely gray
<i>Finger Nails</i>	Usually normal	Frequently brittle, grooved or spooned
<i>Tongue</i>	Normal	Frequently atrophic
<i>Splenomegaly</i>	Rare (Naegeli ²), slight splenomegaly in 10% of cases (Castle and Minot ⁴¹)	Frequent (in 50% of cases (Witts ³⁵))
<i>Gastric Secretion</i>	Amount of free HCl may be increased, normal, reduced or absent	Frequently post-histamine achlorhydria (in 60% of cases (Wintrobe and Beebe ³⁸))
<i>Blood</i>	Leukocytes normal, often increased Platelets normal, frequently greatly increased	Normal, frequently reduced Usually reduced, occasionally normal (Dameshek ^{36 42})
<i>Bone Marrow</i>	Normal (Naegeli, ² Grawitz ⁴³) or hyperplastic (Lee and Minot ⁴⁴)	Always shows normoblastic hyperplasia (Kaznelson, Weiner and Reimann, ⁴⁵ Dameshek ⁴⁶)
<i>Thrombophilia</i>	In 2 to 3% of cases	None

many respects from primary hypochromic anemia. The most striking hematologic feature is the frequently encountered thrombocytosis which behaves in a characteristic manner under iron therapy. The thrombocytosis is characterized by the presence of numerous small, easily agglutinating platelets which create a condition predisposing to the development of spontaneous venous thrombosis and embolism.

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THE LIFESPAN OF THE ERYTHROCYTES ¹

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IN anemia following bleeding or after the administration of phenylhydrazine, J H Pratt and P Morawitz in 1908 noted an increase in the resistance of the erythrocytes. During the stage of advance of the anemia and during the first period of the restitution of the red cells, the limits of the maximal and minimal fragility were shifted in such a manner that erythrocytes less fragile than normal appeared and the most fragile erythrocytes disappeared. Pratt, in collaboration with S Itami, continued these studies and found a considerable increase in the volume of the stroma of the erythrocytes during the phase of high resistance. This condition has been termed pachydermia of the erythrocytes by Morawitz.

In these studies Pratt touched the problem of the lifespan of the erythrocytes, our knowledge of which has not been advanced since. By counting the reticulocytes and analyzing the oxygen consumption of the erythrocytes, we can determine the presence of younger red cells in a manner approaching a quantitative measurement. By determining the osmotic fragility, which increases with age, we are able to get information on the age and the process of aging to which the erythrocytes are subjected. For this latter purpose we employ the method of L Chanel, J L Hamburger, and I Snapper which consists in determining the fragility by counting the number of erythrocytes undissolved in a series of concentrations of sodium sulphate solution.

In the organism, erythrocytes are destroyed by phagocytosis preceded by wear and tear, rather than by hemolysis. However, osmotic fragility indicates the aging process and can be taken as a quantitative measure, the units of which, namely, the concentrations, unfortunately cannot be related or transformed into units of time.

It is unknown whether the lifespan of the erythrocytes is shortened or lengthened in anemia. In the event that the lifespan of the erythrocytes is shortened, this shortening would contribute to the degree of the anemia, in the event that the lifespan is lengthened, this lengthening would compensate for the poor formation of the red cells.

In studying the osmotic fragility in anemic conditions, we rediscovered some findings made by Pratt and his co-workers. In anemia following hemorrhage, in pernicious anemia, and during the recovery period from these conditions, we found the least resistant groups of cells (i.e., oldest groups) absent, as indicated in the following protocols (tables 1, 2 and 3).

As shown in these illustrative examples, erythrocytes disappear before they approach the highest degree of osmotic fragility.

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TABLE I
Case of Duodenal Ulcer Hemorrhage
% Na₂SO₄

Date	19	18	17	16	15	14	13	12	11	10	9	8	7	Millions Erythrocytes per c c
IX 11						14	29	63	76	96	99	100		24
IX 15							21	42	67	88	95	98	100	19
IX 18		4	12	23	27	23	50	63	77	87	96	100		24
IX 30		4	7	10	39	57	68	84	97	99	99	100		46
IX 10				30	35	39	58	79	99	99	100			47

TABLE II
Case of Pernicious Anemia Treated With Liver Extract
% Na₂SO₄

Date	19	18	17	16	15	14	13	12	11	10	9	8	7	Millions Erythrocytes per c c
III 10					7	9	11	32	71	83	91	97	100	24
III 11						3	7	27	46	66	91	95	100	19
IV 24			2	18	31	38	53	65	83	91	100			46
V, 1			5	7	19	29	44	66	83	94	100			47

In anemia following hemorrhage there is no reason why destruction of erythrocytes should occur on a greater scale. From these observations it is evident that under the circumstances there is certainly no delay in the destruction of the erythrocytes and no prolongation of their existence. Therefore, it is reasonable to assume that the rate of destruction of the erythrocytes does not differ from the normal. Normally the daily production of erythrocytes equals the destruction (denominated as a), thus guaranteeing the constancy of their number. In any period of anemia in which restitution of the red count takes place, blood formation is increased up to about 100 per cent of the normal (i.e., to $2a$). If the average span of life of the erythrocytes is denominated as b , the whole number of the red cells is ab . Normally this figure is composed of groups of red cells equal in size but differing in age. When, by increased blood formation, the younger groups become larger ($2a$), the age groups are no longer equal. As blood destruction goes on at the same rate and each group is reduced equally by the hemorrhage, the oldest group is too small to cover the rate of destruction. Therefore, destruction must take place in the group next in age to the oldest.

Discussion of Table IV

1 Before hemorrhage, 5000 c c of blood are present The blood count is 5 million per c c The whole blood holds 25×10^{12} , and 1 liter contains 5×10^{12} erythrocytes

2 The erythrocytes are divided into 10 groups of different age Before the bleeding each group holds 0.5×10^{12} erythrocytes per liter and after the bleeding, 0.3×10^{12} The vertical columns show the composition of the blood in age groups during recovery The lifespan of the erythrocytes is assumed as 50 days

3 Normal formation and destruction of blood in 5 days $= 0.5 \times 10^{12}$

The erythrocytes formed during the recovery from anemia are aging, as shown in the table marked by the dark lines Thirty days after the hemorrhage, the blood contains 6 groups of red cells rather than 10 of different age, the older ones having disappeared After the thirtieth day, the recently formed erythrocytes enter the zone of destruction

As far as fragility is concerned, the findings in table 4 parallel the experimental findings demonstrated in table 3 While a restitution of the red blood count is finished within 20 days after hemorrhage, the restitution of the normal age groups of the red cells takes 70 days

The absence of the red cell groups made up of older erythrocytes in anemic conditions can be understood from the character and the action of the red cells

As the erythrocytes have no nuclei, no metabolism and no facilities for repair or for reproduction, they can hardly be considered as living cells Their main constituent, hemoglobin, performs its function of binding and releasing oxygen in the same manner when separated from the corpuscle, simply as a chemical compound The red cell is nothing more than a chemical machine and as such is subjected to wear and tear

The stress on the erythrocytes is evidently due to their function Binding and releasing oxygen is not only a chemical process, restricted to the quality of the hemoglobin, but concerns the red cell as a whole By taking up CO_2 from the tissues into the blood, chlorides and water enter the erythrocytes in order to maintain the osmotic as well as the acid-base equilibrium Thus the erythrocytes grow larger and assume a different shape The opposite process takes place in the lungs By this continuous process of hydration and dehydration, the stroma of the erythrocytes deteriorates The deterioration is noticeable by the decrease in the size of the erythrocytes and by their increased fragility

In anemic conditions a smaller amount of hemoglobin and a smaller number of erythrocytes have to carry the same amount of oxygen into the tissues Regardless of whether the release of oxygen in the capillaries, i e., the arterio-venous difference, is enlarged, or whether the erythrocytes are carried around more rapidly, the stress on the red cells is greater

The particular items are as follows 1 gm hemoglobin at 0° and 760 mm pressure binds 1.34 c.c. of oxygen (these figures are sufficient for comparison) Normally the blood contains 700 gm of hemoglobin Therefore, the arterial blood (350 gm of hemoglobin) is capable of binding about 500 c.c. of oxygen If the oxygen consumption in 24 hours is taken as 400 liters, and arterio-venous difference in oxygen saturation as 30 per cent, the erythrocytes have to act 2400 times in 24 hours in the double process of binding and releasing oxygen In anemic conditions this figure increases corresponding to the deficit of hemoglobin Thus erythrocytes are worn out faster With the number of actions, the stroma of the erythrocytes undergoes a continuous alteration, which after a definite number of these actions results in a state of inertia Every colloidal structure is subjected to this alteration, which, usually, is termed syneresis Erythrocytes with an outworn stroma are unfit for the process of hydration and dehydration, less permeable for gases as well as for water and ions, and ready for destruction even before they approach the highest degree of osmotic fragility

Thus it is evident that the lifespan of the erythrocytes cannot be measured in units of time, but only in number of actions The smaller the number of the erythrocytes, the larger the oxygen consumption, the shorter the lifespan of the red cells

The old and popular conception that by bodily exercise, outdoor life and high altitude blood is more rapidly renovated, is in complete harmony with these facts and their interpretation

THE MINNEAPOLIS GIANT ~

By H GRAY, *San Francisco, California*

GIANTS are not only dramatic to the layman as extreme variations of the human being, but valuable for the study of growth. In this respect they afford a considerable quantity of evidence which can profitably be analyzed in comparison with normal proportions, particularly of the extremities.

CASE REPORT

J A, a single white male of 46 years, may be called the Minneapolis Giant, after his birthplace. He was admitted to Lane Hospital November 1, 1936, with the chief complaint of foot ulcers of four years' duration.

Family History His father's father, the Norwegian Giant, was reputed to be 2520 mm in height (8 ft 4 in), while the father's own height was variously stated by the patient as 2286 mm (7 ft 6 in) and 1930 mm (6 ft 4 in), and the mother as 1880 mm (6 ft 2 in), there was one sister of normal size. The father died at 41 years of pneumonia, the mother at 32 also of pneumonia, the sister is alive.

Residential History Born in Minneapolis in 1890, he left there at two years for North Dakota, and at nine years started traveling in shows, all over the United States, and, according to his story, to Hawaii 14 times, to China several times, Australia twice, Europe twice, South America once. He has made Los Angeles and San Francisco his home for 13 years.

Occupation Carnivals, circuses, movies, shows, vaudeville, so many that he cannot remember the names of any except Harold Lloyd's "Why Worry?" in 1923, in the advertising for which he was claimed to be the second tallest man in the world. This claim would seem to indicate insufficient information about other living giants, which information, to be sure, is hard to get. For four years he has been unfit to work because of the ulcers on his feet.

Habits Very irregular. His sleep has been irregular and lately troubled with insomnia. Exercise has been minimal during the last four years because of the ulcers on his feet, so that he has spent most of his time sitting around. Drugs in any form are denied. Alcohol he drinks only occasionally and has never been an habitual drinker, though on October 30, 1936, he was arrested by eight policemen because he acted a little peculiarly, having consumed by his account "maybe five or six cases of whiskey." In jail his breakfast, according to the lieutenant, consisted of two gallons of coffee, and he admits being an inveterate coffee drinker, sometimes making it his entire meal and taking eight cups a day. Tea does not interest him. Also he is an habitual smoker. Lately he has been taking patent tonics to "build up his blood." His diet has been inadequate during the past four years.

Medical History Diseases, injuries, operations nothing significant. Questioned by systems, the points of possible interest may be reduced to the following.

Head No trauma, frontal headaches once a month during second period of growth at 28, for 15 years noticed that he had to turn his head in order to see toward the outer sides, and this bi-temporal hemianopsia kept creeping inward until about

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five years ago both lateral halves of his fields of vision were almost gone, no progression since

Ears, nose, throat, lungs all negative Teeth all removed 8 years ago Hair on face and body always very scanty Heart slight dyspnea G I appetite always good but never Gargantuan Constipated for years G U Nocturia three times, for years, attributed to drinking a gallon of fluid a day Venereal denied No libido ever Muscular strength never remarkable Nervous system education



FIG 1 The Minneapolis giant, 2134 mm (7 ft 0 in) beside Dr J S M, 1763 mm (5 ft 9½ in net)

ceased at second year of high school, and subsequent learning has been difficult because of poor memory, especially of recent years His disposition he regards as nervous but good, except during 24 hours after attacks These will now be described

About five years ago, say in 1931, he had his first epileptic fit, he was very tired when he went to sleep and during his sleep he thinks he had an attack because when he woke up his tongue was sore His first attack in public was about four years ago when he was standing on a corner waiting for a street car, his body became stiff, teeth ground and he became unconscious for about five minutes, after which he felt

weak and slept for some time. The spells have occurred at intervals varying from two weeks to six months. The latest attack was two weeks before admission, he was sitting in a chair when he slumped over suddenly and fell to the floor unconscious, afterwards he was told that his legs had become rigid and then started quivering. His teeth grind and he thinks he bites his tongue. Never other injury. Never incontinent. He feels sleepy and depressed afterwards.

Olfactory hallucinations, an odor like hard-boiled eggs freshly opened, have been common since the grand mal began. Such uncinate attacks occur in 7 per cent of acromegalics (Davidoff¹).

Enlargement of hands, feet, jaw and lip he first noticed about 1921 at the age of 31, about five years after acromegaly was recognized at the Mayo Clinic. This extraordinary delay in a patient's appreciation of acral enlargement has previously been recorded by Buday and Jancso² (1894) and by Mark³ in his book on his own case.

Weakness began about the time of his second growth at 28, and has become worse in the last five years.

Ulcers began on his feet about 4 years ago. The first was on his right foot, apparently due to an inflammation under a callus, it cleared up. On his left foot the ulcer began about 18 months ago. He has been using crutches or a cane off and on for the last four years. Also there has been a fissure on his upper lip for the last five years, which has refused to heal, and which he attributes to repeated trauma from playing his harmonica.

Weight and Growth History This is shown in table 1.

TABLE I
Growth History

Date	Age	Stature Net		Weight Net		Observer
		mm	ft -in	kg	lbs	
Mar 5, 1890	Birth	Unknown		Unknown		Patient
1898	8	1929	6-0	"ganglv"		
		Began Spurt I				Patient
1908	18	2134	7-0	Unknown		
1915	25			127 0	280	Patient
Nov 23, 1916	26 7	Not stated, acromegalic, genit infant, bi-temp hemianop, sella enl'd		151 5	334	Mayo Cl
		Began Spurt II				Patient
1918	28	He first noticed enl				
1921	31	extrs, jaw, and hp		228 2	503	Patient
		2438	8-0	210 9	465	Patient
1923	33	He noticed loss wt, strength, color		181 4	400	Patient
1930	40	First grand mal				Patient
1931	41					
Mar 7, 1933	43	2154	7-1	136 4	300	San Francisco Hospital
Nov 2, 1936	46 7	{ 2362	7-9	129 3	285	Patient
		{ 2134	7 0	122 0	268	Gray
Nov 9, 1936	46 7			125 4	276	Gray

Physical Examination A veritable giant and obviously acromegalic. Mandible very long and large but protrudes only slightly. Maxillae very prominent as are the supra-orbital ridges. Lips thick. Voice is not deep nor loud but weak. Ears large.

Skin quite pale, somewhat tawny, is coarse but pliable with many wrinkles, it is loose and he has evidently lost weight

Eyes Pupils and movements normal without nystagmus, wears glasses

Fundi Generally pale Veins not especially full No sclerosis of vessels Both discs on medial halves are almost obliterated with irregular, poorly margined portion remaining Both discs in outer halves are pale yellow-white, more marked on left, appearance of optic atrophy

Ears Externally negative Watch heard, both sides, 25 cm vs normal 30

Nose Septum moderately deviated to right, no discharge

Teeth Out Oral mucous membranes moderately pale

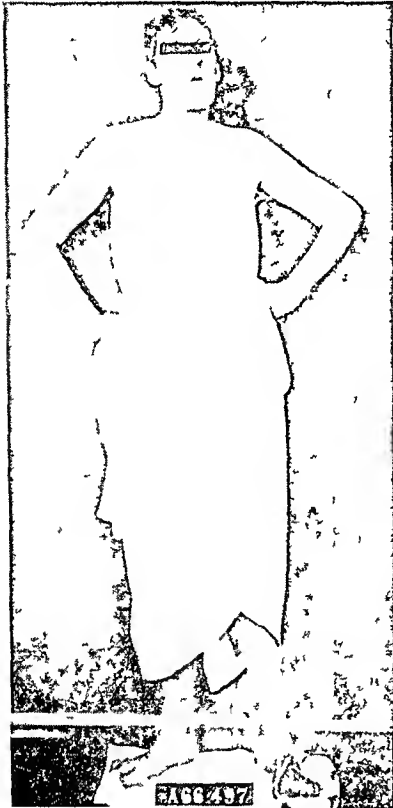


Fig 2



Fig 3

Fig 2 Showing extraordinary claw toes and his characteristic posture and expression

Fig 3 Close-up of face and hand

Tongue Slightly large, no papillary atrophy

Tonsils, throat, neck, thyroid, heart, peripheral vessels, lungs, abdomen all negative

Pulse 54-84 Blood pressure 110 mm mercury systolic and 70 diastolic

Hair On scalp it is dark brown with some gray, fine in texture, normal in amount Brows and lashes normal On face only slight down, last shaved 5 months ago In axilla very thin and silky On chest none Crines scanty with horizontal upper edge On arms none On lower legs slight fuzz

Genitalia Penis small, about 5 cm long, infantile Testes small, soft, about 2 cm long

Rectal Sphincter tone poor, patient complains of great pain in rectum

Prostate Can hardly be felt

Spine No kyphosis, scoliosis, nor lordosis

Extremities Bony with wasted flabby soft parts Hands and feet large, only moderately large in proportion to rest of extremities Single penetrating ulcer on bottom left foot (J D Myers)

Urine Acid, 1010, no albumin, no sugar, no blood, casts or pus

Blood Wassermann negative, RBC 4 57 million, Hgb 70 per cent, WBC 11,100, neutrophiles 68 per cent, eosinophiles 5 per cent, basophiles 1 per cent, lymphocytes 22 per cent, monocytes 4 per cent, and a few days later RBC 4 38, Hgb 68 per cent, WBC 12,350, neutrophiles 68 per cent, eosinophiles 1 per cent, basophiles 0, lymphocytes 28 per cent, monocytes 3 per cent Sugar tolerance Fasting blood sugar 120, $\frac{1}{2}$ hr 160, 1 hr 165, 2 hrs 140 mg per 100 c c, cholesterol 117, urea 27, chlorides as NaCl 435 Van den Bergh direct negative, indirect 0 55 units, icterus index 4 3

Stool Negative

Basal Metabolic Rate Minus 17 per cent, pulse 60-58 Another day minus 11.

Electrocardiogram Sinus rhythm, rate 60, P R 0 17, QRS 0 08 sec, left axis deviation

Vital Capacity 61 liters

Shoes The heels on his shoes are 56 mm (2 2 in), and their weight is 3 2 kg (7 lbs)

Röntgen-Ray A film record was made of this gigantic skeleton The cranium is not enlarged, but its thickness is unusually great, the calvarium measuring nearly 2 cm in most places The jaws are edentulous, the mandible very long The sella is large, measuring about 2 cm backward, and is pretty deep, neither the floor nor the dorsum appear to be suffering from pressure atrophy, the anterior clinoids appear intact, although their structure is not very dense

In the infected left foot no roentgen evidence of osteomyelitis is detected, the right second and third metatarsals have been broken and the second is ununited with dorsal lateral displacement of the toe, this evidently happened a very long time ago

The phalangeal tufts of the big toes are quite unusual in form (figure 4) while in the other toes there is only a slight unevenness of the development of the tufts The tufting of the fingers is distinctly less than average (figure 5)

The heart is well within normal limits for a man of this size

The lungs show some infiltration in both upper lobes, on the right in the second interspace and on the left in the apex and first and second interspaces Also in the first and second interspaces are small areas which look like cavities but may be emphysematous blebs At any rate we have evidence of old tuberculosis in each upper lobe (R R Newell)

Eye Consultation O D 20/70, O S 20/25 Fundi discs markedly pale, vessels and maculae normal Fields bi-temporal hemianopsia, the field cut comes very close, up to about 2° to the macula on the right and to about 5° on the left (M Miller)

Orthopedic Consultation Clawing toes Marked prolapse of heads of metatarsals, especially left foot Chronic ulceration on sole without underlying osteomyelitis Some sensory disturbance Plates seem to be satisfactory Ulcer will probably heal with bedrest and elevation (D S King)

Neurological Consultation Tall individual with acromegalic features Generalized weakness but no paralysis No deep reflexes elicited No pathological reflexes All modalities of sensation intact except over feet and ankles where there is a marked hypesthesia and hypalgesia Muscle position sense in toes fair Cranial nerves Bi-temporal hemianopsia grossly Discs pale Balance of cranials intact Psychologically he is generally cooperative but quite easily irritated especially if obstructed in any way Manner effeminate and some of reactions quite juvenile and immature Sensorium intact I Q is 88 which is dull normal Some scatter shown indicative probably of organic deterioration Patient has expressed suicidal ideas which make



FIG 4 X-ray of foot of patient and of normal, which in this cut is raised to approximately equal magnification for clearer comparison of unusual bony structure



FIG 5 X-ray of hand of patient and of normal, showing relative size and absence of traditional tufting

prolonged hospitalization a consideration Impression 1 Pituitary adenoma with gigantism and acromegaly, destruction now resulting in hypofunction, 2 Epilepsy, symptomatic (J F Card)

Note by Visiting Physician (Nov 2, 1936) The patient is immensely tall, looks somewhat tired and worn and has clearly lost much weight Face has definite but moderate acromegalic appearance with thickening of supraorbital ridges and elongation of jaw Tongue is large Two plates Consistency of skin is thin and smooth There is transverse pubic hair of feminine type, moderate axillary hair, beard practically absent Considerable deposition of fat about hips Testes about 2 cm in length and infantile, penis not obviously abnormal Complete absence always of libido and potentia Heart is fairly large, slow, sounds clear Blood pressure rather low No viscera felt in abdomen There is definite bi-temporal hemianopsia with hand test There is definite grayness of optic discs on both sides Definite impairment of superficial sensation on feet Knee jerks not obtained in bed Definite deformity of feet which he thinks due to high heels Small penetrating ulcer on ball of left great toe, probably connected with this also Cranial nerves other than optic seem intact Impression The sequence of events here seems very clear 1 hyperfunction of alpha cells of anterior lobe, beginning early in life with simple gigantism There has probably been from the start a tumor which has destroyed or inhibited gonad-stimulating cells of pituitary, hence failure of sexual development, feminine habitus, lack of hair, etc 2 The tumor after a period of more or less arrest evidently began to grow again causing acromegaly and pressure on chiasm with optic atrophy and bi-temporal hemianopsia Secondary effects of long-standing acromegaly in form of weakness, anemia, etc, are explainable (A L Bloomfield)

Note on Epileptic Attacks on Ward (Nov 2, 1936) Yesterday afternoon at 4 30 the patient had an epileptic attack, he gave a cry, and was discovered in a generalized clonic convulsion, unconscious, with much grinding of the jaws Unconscious about five minutes, then lost abnormal movements, mentally confused for a few minutes, and fell into deep sleep This morning feels well except "washed out" (J D Myers) Similar attacks at 10 30 a m, Nov 11, 11 a m and 12 15 p m, Nov 13, 1936, but lasting only about half a minute

Diagnoses Giantism due to hereditary hyperpituitarism
 Acromegaly
 Hypopituitarism secondary to acidophile adenoma
 Hypogonadism
 Hypothyroidism
 Low I Q
 Epilepsy
 Uncinate attacks
 Anemia, secondary
 Ulcer of foot
 Claw toes
 Barbed-arrow phalanges
 Tuberculosis, inactive

Treatment The diet was made as ample as the patient would eat and was found to vary from 4000 to 5500 calories, an average day's distribution was C 410, P 140, F 320, calories 5080 Iron was given as ferric ammonium citrate 50 per cent solution, 4 cc t i d p c Liver and stomach concentrate was administered in the form of Extralin (Lilly & Co) capsules, each 0.5 gram, 2 t i d a c, which for the 24 hours is equivalent to 120 grams of fresh liver Adrenal cortex extract seemed indicated but before any was obtained the patient left the hospital on Nov 14 Thyroid extract (Armour & Co) 0.13 gram daily, was begun on Nov 7, and after four days the patient stated that his feet felt warm and sensitive for the first time in years

Limitation of the activity of the eosinophilic cells of the anterior pituitary by operation was proposed to Dr F L Reichert, but it was agreed to postpone surgical treatment until the general vigor could be improved. Radiation likewise was deferred, owing to the probability that the patient would leave town shortly so that follow-up would be inadequate.

After-History Jan 15, 1937, committed to Mendocino State Hospital

STUDY OF BUILD

Anatomical Measurements The build of this giant with acromegaly and hypogonadism (often called by the ambiguous term infantilism) may be documented by the following figures and tables. Although eager for relief the patient was, like most giants, resistant to tests in general and measurements in particular, after meals and gifts of tobacco he became slightly less suspicious, and after the ego had been elevated by lavish deference, could finally be coaxed into transient assent. Comparisons of his build with normals may conveniently be treated under four main headings, stature, general set of anthropological measurements, extremities, and miscellaneous measurements.

Stature Comparisons Humberd ⁴ (1936) had "never been able to find an absolutely reliable account of a human being who has ever attained as much as 8 feet (244 cm) in height." Although he has tilted so persuasively at some reported data, as have others before him, there remain a number of undisputed taller giants (table 2).

TABLL II
The Taller Giants

Gallatin Giant	Lackey ⁵ 1899	2591 mm
Irish Giant in Trinity College, Dublin	Cunningham ⁶ 1891	2590 mm
Alton Giant Wadlow	Barr personal commun 1936, this suggests that he had developed some kyphosis when seen by Humberd in 1937 ⁷	2559 mm
Austrian Giant	Topinard ⁸ 1885	2550 mm
Giantess Wehde	Ranke, cited by Launois and Roy ⁹	2550 mm
St Petersburg Giant skeleton	Cushing ¹⁰ 1912	2540 mm
Kalmuck Giant in Orfila Museum, Paris	Topinard 1885	2530 mm
Alton Giant Wadlow	Humberd ⁷ 1937	2521 mm
Giant Byrne, or O'Brien	John Hunter, cited by Cunningham ⁶	2490 mm
Giant Wilkins	Dana ¹¹ 1893	2450 mm
Minneapolis Giant, the present case		2134 mm

General Anthropological Comparisons The giant's data are shown in table 3, columns 1 to 3. When we look for control series of measurements on tall, American born, normal, white men we find in no one place any set of dimensions complete. For the set used in our general routine study of build we chose the averages on the tallest group, namely 109 football

TABLE III
Anatomical Measurements, Routine, Metric and without Clothing

Measurement		Giant (3)	Football Players		Coef G/FB (6)	Dev /SD (7)	Expected Frequency (8)
(1)	(2)		Mean (4)	SD (5)			
Weight in kg	W	122.0	77.3	9.3	1.58	4.8	0.8/10 ⁶
Stature in mm	S	2134	1780	74.0	1.20	4.8	0.8/10 ⁶
Sitting height	Si	1090	929	33.9	1.17	4.7	1.3/10 ⁶
Chest circumf	C	1170	925	54.5	1.26	4.5	3/10 ⁶
transv	T	394	304	18.1	1.30	5.0	0.3/10 ⁶
ant post	AP	260	228	15.4	1.14	2.1	18/1000
module	ChM	327	268	15.0	1.22	3.9	48/10 ⁶
Shoulder bi-acr	BA	472	394	20.7	1.20	3.8	72/10 ⁶
Pelvis bi-crist	BC	408	292	13.3	1.40	8.7	1.6/10 ¹⁸
Head length	L	216	199	7.0	1.09	2.4	8/1000
breadth	B	164	156	4.8	1.05	1.7	
height	OH	138	135	5.1	1.02	6	
module	CM	173	163	3.9	1.06	2.6	5/1000
Face height	MN	160	127	5.5	1.26	6.0	0.01/10 ⁶
breadth	BZ	160	142	5.0	1.13	3.6	0.2/1000
module	FM	160	134	4.1	1.19	6.3	
Nose height	NH	72	57	3.9	1.26	3.8	72/10 ⁶
breadth	NB	38	36	2.2	1.06	9	
Above items in per cent of stature	W/S	57.2	43.3	4.9	1.32	2.7	3/1000
	Si/S	51.1	52.1	1.1	.98	— .9	
	C/S	54.8	52.1	3.4	1.05	.8	
	T/S	18.5	17.2	1.1	1.08	1.2	
	AP/S	12.2	12.8	1.0	.95	— .6	
	ChM/S	15.3	15.0	.9	1.02	.3	
	BA/S	22.1	22.1	1.1	1.00	0	
	BC/S	19.1	16.4	.7	1.16	3.9	48/10 ⁶
	L/S	10.1	11.2	.4	.90	— 2.8	3/1000
	B/S	7.7	8.7	.4	.89	— 2.5	6/1000
	OH/S	6.5	7.6	.3	.86	— 3.7	1/1000
	CM/S	8.1	9.2	.3	.88	— 3.7	
	MN/S	7.5	7.1	.4	1.06	1.0	
	BZ/S	7.5	7.9	.4	.95	— 1.0	
	FM/S	7.5	7.5	.3	1.00	0	
	NH/S	3.4	3.1	.2	1.10	1.5	
	NB/S	1.8	2.0	.1	.90	— 2.0	
Index chest	AP/T	66.0	74.2	4.9	.89	— 1.7	
trunk breadth	BC/BA	86.4	74.3	4.1	1.16	3.0	1/1000
cephalic	B/L	75.9	78.3	3.5	.97	— .7	
facial	MN/BZ	100.0	89.9	4.8	1.11	2.1	18/1000
face/head L	MN/L	74.1	63.9	3.3	1.16	3.1	1/1000
face/head B	BZ/B	97.6	90.9	2.7	1.07	2.5	6/1000
nasal	NB/NH	52.8	64.6	6.1	.82	1.9	

players whose average height was 1780 mm (70.1 inches). Since these appeared in a publication inaccessible in many medical libraries,¹² the essential averages and standard deviations are reprinted in columns 4 to 5. A coefficient is calculated in the next column, (6), by dividing the giant by the normal, for example, the coefficient for stature shows that the giant is 20 per cent above the normal. Another method, more elaborate, but more refined, is to take the deviation of giant from the control and divide this by

the standard deviation (Dev /SD) as done in column 7, and to interpret this for the significant results, I have shown in column 8 how small a proportion of the population may be expected to show such extreme values, that is, if the distribution of giants follows the normal Gaussian law. Apparently it does not. Taking stature for an instance, the probability expected is seen to be 0 000,000,79, say, 0 000,001, hence in the United States with a population of over a hundred million people we should have more than 100 men as big as the Minneapolis giant, and certainly no such number has become known.

Extremities Comparisons Acromegaly In assessing the presence or absence of acromegaly, clinical practice might be made more objective by measurements aimed to determine whether the size of the organ, either absolutely, or better relatively to stature, is remarkable compared to that usual in normals. In the literature are scattered lengths and circumferences of such parts of the frame as happened to look extraordinary, usually without adducing control values from the literature or—when such do not exist, as is the case for many of the measurements taken—without supplying a single control. Clinical anatomy requires comparisons.

For the jaw, which it is true is hard to measure, the data are scantiest, and then by methods which are hard to apply in the living. By the method which is best to my mind, the radial distance from the earhole to the tip of the chin, what may be termed the chin radius or porion-menton, all that I can find are the following:

	mm	/S	Giant/Norm
Normal 1820 mm (71 7 in.)	128	7 03	
Minnesota Giant	155	7 26	1 21 = 21% excess
S B. of Buday and Jancso ²	180	9 09	1 41 = 41% "
R S. of Pentagna ¹³ 1932 (child 11 yrs.)	120	9 09	

Foot length will be treated briefly since (1) so much more material is available for the hand, and (2) our giant's foot, while of course large absolutely, is when referred to stature (FL/S) actually smaller than normal.

	mm	/S	Coef Giant/Norm
Minnesota Giant	306	14 3	1 17 absolutely
245 Old Americans of Hrdlicka ¹⁴ (1925) of average stature 1744 mm	261	15 0	95 relatively

Hand Size Methods have been exhaustively detailed by Bayer and Gray,^{15, 16} 1933 and 1936. In the present connection the most illuminating ideas are suggested by considering hand length referred to stature (100 HL/S). Since this relationship is smaller the taller the person, the ratio is plotted against stature in figure 6. Normal means (maltese crosses) for

increasing heights according to Bach¹⁷ have been spotted and a line fitted by eye to show the general trend. The variability of individuals is indicated by plotting 16 white males (simple crosses) (unpublished data). The Minnesota Giant is located (solid black spot). Other giants from the literature have been collected (open circles), these may be considered under several heads.

The extraordinary Alton Giant (double circles)⁷ is seen at three ages—12, 13, and 18 years. Clearly he was first a simple giant and later developed acromegaly.

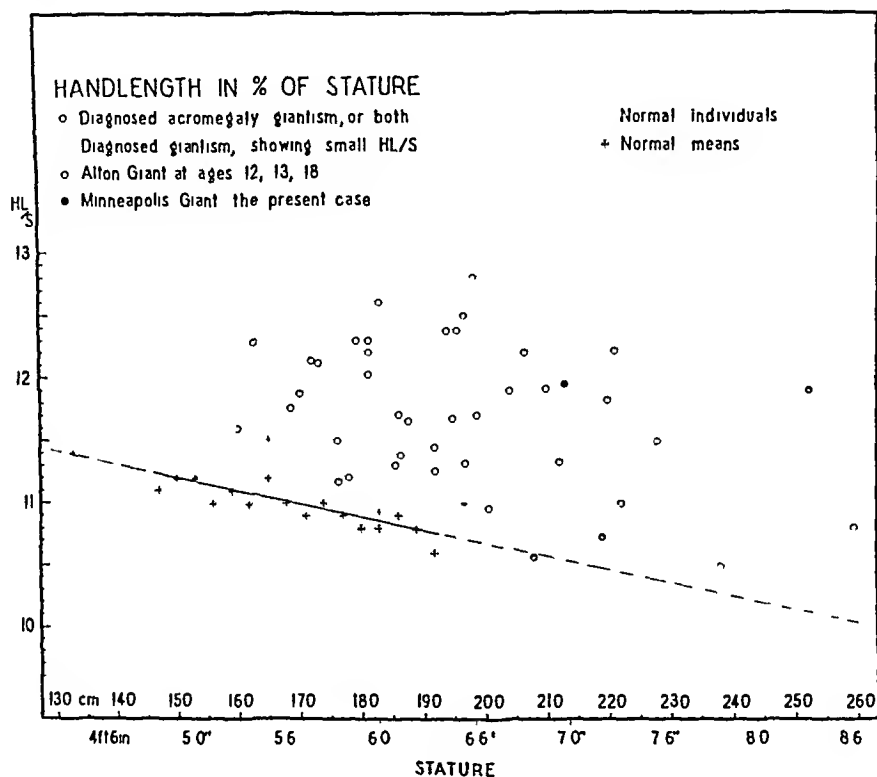


FIG 6 Relative hand-length (HL/S) plotted against stature

A paradoxical group is next noticed: diagnosed giants and revealing ratios actually smaller than normal (small circles). Out of 45 giants there were 5 such, or 11 per cent. Incidentally the two juvenile giants bore the additional diagnosis of precocious puberty. Listing them in order of increasing stature we get table 4.

A group with such incredibly large values for this ratio HL/S that they would lie far above the nearest point on the diagram (therefore not inserted) are

		S	HL/S
R S	Pentagna 1932	1320	13.6
F V	Pel ¹⁸ 1906	1720	18.3

TABLE IV
Giants with Paradoxically Small Hands (HL/S)

		S	HL/S
K K, aged 8	Linser ¹⁹ 1903	1380	10.9
C H, aged 6	Hudovernig and Popovits ²⁰ 1903	1400	10.4
Wurzburg Giant	Bassoe ²¹ 1922	1920	10.5
P C	Bonardi ²² 1899	1940	10.1
American Giant	Hinsdale ²³ 1898	2286	10.9

The main group consists of persons diagnosed giantism, acromegaly, or both (larger circles), their locations warrant the important conclusion that 89 per cent of giants are in fact acromegalic.

Hand Proportions in Detail A more refined comparison, partly as a

TABLE V
Anatomical Measurements of the Hand

Measurement (1)	(2)	Giant (3)	16 Normals Mean (4)	Coef (5)
Ray I	I	183	140	1.31
Ray II	II	247	184	1.34
Ray III	HL	255	192	1.33
Ray IV	IV	246	182	1.35
Ray V	V	222	158	1.41
Midfinger length	FL	134	96	1.40
Palm length	PL	121	96	1.26
Hand breadth	HB	114	86	1.33
Bi-styloid br	Bs	78	59	1.32
Hand circumf	HC	251	210	1.20
Palm circumf	PC	254	219	1.16
Wrist circumf	Wr	195	167	1.17
Above items in per cent of stature	I/S	8.6	8.0	1.08
	II/S	11.6	10.6	1.09
	HL/S	11.9	11.1	1.07
	IV/S	11.5	10.5	1.10
	V/S	10.4	9.1	1.14
	FL/S	6.3	5.5	1.15
	PL/S	5.7	5.5	1.04
	HB/S	5.3	5.0	1.06
	Bs/S	3.2	3.4	.94
	HC/S	11.8	11.9	.99
	PC/S	11.9	12.5	.95
	Wr/S	9.1	9.6	.95
Above items in per cent of hand length	I/HL	71.8	72.7	.99
	II/HL	96.9	95.9	1.01
	IV/HL	96.5	94.6	1.02
	V/HL	87.1	82.3	1.06
	FL/HL	52.6	50.0	1.05
	PL/HL	47.5	49.9	.95
	HB/HL	44.7	45.0	.99
	Bs/HL	27.1	29.8	.91
	HC/HL	98.4	105.4	.93
	PC/HL	99.6	114.4	.87
	Wr/HL	76.5	85.3	.90

matter of record, partly as a matter of method, can be given, based on 16 normal white males, for most of the measurements, though on only 7 of them for the items Bs, HC, PC, Wr. The principal conclusions are these. In absolute measurements the giant is over 30 per cent larger than the average for this particular sample of 16 normals. The measurements related to stature make allowance for the greater stature of our subject and are therefore more useful, they are given in the second panel of the table. They show that the giant's hand is larger relatively to his size than is the case with normals, with the exceptions that the circumferences of hand and wrist are smaller relative to height than is the case with normals. An acromegalic with the broad type of hand would perhaps yield circumferences relatively larger than normal. The measurements related to the size of the hand, as judged by the length of the central ray or hand length, is given in the third panel of the table, the index, ring, and little finger rays are all more nearly the length of the midfinger ray than is the case in normals, the thumb ray, however, is abnormally short. The data are in table 5.

Miscellaneous Comparisons. For the miscellaneous items put on record in table 6 satisfactory controls have not been found. In order not to extend

TABLE VI
Miscellaneous Measurements

			mm	/S
<i>Head</i>				
	Circumf		620	29.1
<i>Ear</i>				
	Length	EL	77	3.6
	Breadth	EB	37	1.7
<i>Lip</i>				
	Slit		57	2.7
	Thickness		16	0.8
<i>Span</i>		Sp	2190	102.6
<i>Lower Length sym-sole</i>		LL	1140	53.4
<i>Upper Length v-sym</i>		UL	994	46.6
<i>Arm</i>				
	Upper	ac-r	411	19.3
	Lower	r-sty	334	15.7
<i>Leg</i>				
	Upper length	tro-ti	720	33.7
	breadth	bi-cond	136	6.4
	Lower length	ti-sph	460	21.6
	breadth	bi-mal	87	4.1
<i>Foot</i>				
	Length	FL	306	14.3
	Breadth	FB	110	5.2

comparisons tediously, they may be ended with an examination of the relative growth of the three segments of the upper extremity—upper arm, lower arm, and hand length. In the present giant the overgrowth is least marked in proximal segment, next in the forearm, and most in the distal segment the hand. The analysis is given in table 7, in which as controls (column 4) I have copied the dimensions for the tallest group, stature 1920

TABLE VII
Relative Overgrowth of the Several Segments of the Arm

Segment (1)	Giant		Normal		
	mm (2)	% of Total (3)	mm (4)	% of Total (5)	Coef (6)
Upper	411	41.1	373	43.7	0.94
Lower	334	33.4	277	32.5	102.8
Hand	255	25.5	203	23.8	107.1
Total	1000	100.0	853	100.0	

mm, in Bach's table, then I have figured each segment as a percentage of the total extremity (columns 3 and 5), and finally divided the giant by the normal (last column), with striking emphasis stated, namely, the more distal the segment, the greater the degree of overgrowth

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ORGANIC DISEASE OBSCURED BY NEUROTIC BEHAVIOR¹

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THE frequency of neurotic behavior in patients seen in general medical practice, the difficulties met in making accurate diagnoses and in caring for such patients, the present interest of physicians and surgeons in this subject as shown by their writings and discussions, and the increasing number of patients labelled "neurotic," emphasize the importance of critical evaluation of emotional states in the sick.

Symptoms of neurotic origin simulating true organic disease, but without demonstrable lesion, are common. Neurotic behavior, however, may follow or be intensified by organic disease, or such behavior may exist in the presence of organic lesions, in an apparently unrelated way. The patient is a total personality, and responds to intrinsic as well as extrinsic factors. It is therefore of great importance that we constantly remain aware of the possibility that symptoms may precede for months, even years, the discovery of a slowly developing organic lesion, screened and obscured effectively by neurotic behavior, as is demonstrated in the following reports.

Case 1 An unmarried Jewess, 38 years old, complained of inability to walk. Fifteen years ago she had attacks during which she would scream, jump, stamp her feet, and become otherwise uncontrollable. She had always shown great pride, independence, jealousy, sensitiveness, explosive outbursts of temper, and a strong love of children. She had had an appendectomy, a right nephropexy, and a partial oophorectomy for dysmenorrhea.

For six years she had been under constant influence of self-administered sedatives because of sacral pain recently referred into the right posterior thigh unrelieved by tonsillectomy, hydrotherapy, heliotherapy, and psychotherapy including attempted hypnosis. She became lame nine months ago, falling several times.

Eight months ago there was flaccid paralysis of both lower legs. Vibratory sensation was impaired over the right tibia and ankle joint. Pain, touch, and temperature were denied completely over the sole of the right foot, and partially below the right knee. Laboratory findings were normal. The history of previous medication, an obvious toxic state, and complete reactions of degeneration below the right knee, warranted a provisional diagnosis of toxic neuritis at that time.

Five months ago an abortive right ankle clonus appeared. Four months ago the thigh muscles bilaterally showed increased tonus. Shooting pains in the lower lateral thighs, referred into the lumbar spine, became more severe, appeared oftener, and were associated with sudden intense contractures of the thighs on the hips. Occasional urinary and fecal incontinence developed. Three months ago right ankle clonus persisted. Continued spasticity in the thigh muscles appeared with paroxysmal spastic contractures, occurring every 10 to 15 minutes. The right knee jerk became increased. Sensory loss developed in the distribution of the twelfth dorsal, the lumbar, the first and second sacral spinal nerve segments. Another spinal puncture now revealed golden yellow fluid, strongly positive for globulin. A diagnosis was

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made of extramedullary spinal cord tumor. Laminectomy revealed the tumor extending from the eighth to the twelfth thoracic vertebrae. It was successfully removed.

Since operation there has been improved sensation and use of the lower extremities. The patient's behavior, however, has remained typically neurotic. After the provisional diagnosis of toxic neuritis was made, eight months' continuous observation was necessary to establish a correct diagnosis. It had been necessary also to make repeated neurological examinations in order to sift out of a galaxy of bizarre symptoms and signs the above changes dependent upon the organic lesion.

Case 2 A housewife, 38 years old, complained of nausea, emesis, headache, diplopia, diffuse muscular soreness and aching pain in the left shoulder. For a year there were intermittent attacks of numbness and partial loss of strength in the left hand and forearm. For two months there had been intermittent weakness. She had become unconscious twice.

She had always been nervous. Nausea was felt when she heard unpleasant noises. She worried about a possible developing arthritis, uterine cancer, her husband's health, and financial losses. Eight years before she had collapsed following her husband's nervous breakdown. She had had yearly attacks of influenza since 1918. A four year old son, hyperactive and mischievous, caused constant anxiety. A year before she was in an automobile accident which produced great shock. Four months before she had had an acute attack of tonsillitis with subsequent tonsillectomy and post-operative hemorrhage requiring sutures.

The only positive physical finding was a transient bilateral squint which she said had been present since childhood.

After six weeks there was twitching of the muscles in the upper left face and intermittent occipital headache. A week later there was numbness in the left face, and rapid loss of power in both lower legs. She then recalled a similar, first attack which had occurred seven months ago. There was now a beginning neuroretinitis, and decreased sensation in the mandibular branch of the left fifth cranial nerve. She also recalled an attack of clonic contractures in the left upper arm with severe left cervical pain. The spinal fluid was under 56 mm mercury pressure. Other laboratory findings were normal.

A neurosurgeon found no definite evidence of an organic lesion, but requested that she return again in six weeks. Craniotomy then revealed "a very deep glioma of the parietal lobe."

Thus, we see that an emotional fog had successfully obscured the three cardinal features of a brain tumor.

Case 3 A Russian Jew, aged 49 years, complained of diffuse headache for two months, worse at night and when coughing. He had been a professional boxer, and drank alcohol to excess. He was much depressed, cried, worried about financial losses, and slept poorly. There was pain in the lower anterior chest, and for three weeks clotted blood was observed in his sputum. He had been told four months ago that he had heart trouble.

His pupils reacted sluggishly, incompletely and irregularly. His blood pressure was 160 systolic and 100 diastolic. The cardiac apex was palpable in the fifth interspace 2 cm to the left of the left midclavicular line in the recumbent posture. Finger to finger test showed past pointing. Roentgenograms disclosed a dense shadow occupying the greater portion of the left lung field, appearing nodular under the fluoroscope. The heart, aorta and trachea were displaced to the left. The appearance suggested a new-growth.

Patient returned home for a week, developed a hemiparesis, and was taken to a clinic where bronchoscopic examination revealed a lesion involving the left main bronchus. The growth bled easily. It was clinically considered malignant, although a biopsy showed only inflammatory tissue. An intracranial metastatic growth was also considered to be present, and he died a few weeks later.

Business reverses suggested a cause for complaints in a patient, who for several years had sought escape from unpleasant facts in alcoholic sprees. Roentgen-rays of the chest and bronchoscopic findings finally established an organic basis for his illness.

Case 4 A married woman, 31 years old, began to complain two years ago of agonizing rectal pain aggravated intensely by defecation. Nine months ago she had recovered from influenza, and roentgenograms of her chest had shown enlarged hilar glands to which an elevation of temperature was attributed. She was finally taken to a neuropsychiatrist, who learned that her husband had been without a position for six months. Their mortgaged home might be lost. A nine year old son, with cerebral spastic diplegia, required constant care which could not be hired. Her husband's parents had little sympathy for their predicament. She had given up her study of music to which she had been devoted. Her husband accepted his parents' opinion even concerning routine household matters. She was sent away for treatment of her nervous state. She was in a hopeless, puzzled, depressed state of mind, her mental anguish probably worse than her exquisite, constant rectal pain. Examination showed a tender rectal mucosa exuding pyoid material. Complete relief of pain followed excision of a perirectal abscess and hemorrhoids.

Explanations to the patient and interviews with her husband directed toward increasing his understanding of her situation and the necessity of institutionalizing their child have enabled the patient to adjust herself to her situation and return home.

On physical examination, a perirectal abscess was found to have caused the pain which for two years was believed to be of neurotic origin.

SUMMARY

Neurotic behavior may mask organic disease so that it is unrecognized. In caring for the neurotic patient, it may be necessary sometimes to withhold judgment and examine the patient repeatedly in order to establish conclusively a correct diagnosis.

RELATION OF ERYTHEMA NODOSUM AND RHEUMATIC FEVER; A CRITICAL SURVEY

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THE etiology of erythema nodosum has been a source of considerable controversy which has not abated, despite the acquisition of what is considered to be fresh and decisive knowledge on certain aspects of the subject. The point of view expressed will often depend on the nature of the branch of medicine practiced and the country from which the report emanates. Broadly envisaged, there are four principal schools of thought: (1) those who regard erythema nodosum as a specific independent entity, in this group are ranged the dermatologists (Tachau¹) and an occasional internist (London's nodal fever²), (2) those who consider it to be chiefly, if not entirely, dependent on the factor of tuberculosis, in this category are to be found the pediatricians, (3) those who are of the belief that the eruption represents one of the rheumatic manifestations proper and, as a sub-class, those who are of the opinion that the skin lesions are of streptococcal origin, this group is composed preeminently of internists, (4) finally, there is an eclectic category of observers who consider erythema nodosum as attributable to a variety of causes, using as its chief argument the point that the rash has been encountered in the course of a host of maladies.

The principal purposes of this critical survey will be: (1) To discuss in some detail the alleged relation between erythema nodosum and rheumatic fever, a view which has numerous adherents today. While it cannot be denied that skin lesions of this type may be encountered under certain circumstances in the course of rheumatic fever, it appears that the data compiled in the past to substantiate this association are subject to much valid criticism. No attempt will be made to review the interesting streptococcal hypothesis, as the data which have come to light are too meager and inconclusive as yet. (2) To point out that the establishment of the diagnosis of erythema nodosum is by no means a simple procedure in all instances, and that the morphologic attributes of this eruption and of others simulating it are in want of further study and of critical analysis. Much of what has passed as erythema nodosum belongs, in reality, to another category of disease. It is apparent that in the pursuit of this problem the cooperation of the dermatologist with the other branches of medicine would be mutually profitable.

HISTORICAL ASPECTS

In the middle of the nineteenth century erythema nodosum was generally classed as "arthritic" or "rheumatic." In 1859 G. See³ concluded, on

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the basis of clinical observation, that the joint pains encountered in this affection differed from those observed in rheumatic fever, that they represented a special type of arthralgia occurring before, during, or after the appearance of the eruption, that they were not characterized by redness of the overlying skin and swelling of, or serous effusion into, the affected joints, and, finally, that the articulations were capable of active and passive motion. It was also known at this time that the use of anti-rheumatic drugs was generally without avail. Trousseau⁴ was of the belief that erythema nodosum was a specific disease, separating it from rheumatic fever since, as he stated, "I have never seen redness or swelling in the situation of the affected parts, nor have I ever found signs of cardiac lesion." Bailow,⁵ on the basis of extensive observations in children, remarked that, "Erythema nodosum, it is well known, is associated with severe pains in the limbs and some fever and is sometimes followed, as rheumatism is, by considerable anemia. But I have never been able to assure myself of the production of an organic murmur in this disease, nor of any intercurrent arthritis, however slight, and it seems possible that the pains in the limbs may be accounted for, in great measure, by the effusions which, though limited in amount, often occur in spots which do not readily yield as on the front of the shins." Harrison⁶ pointed out that erythema nodosum does not, as a rule, recur whereas this is a striking characteristic of rheumatic fever. Garrod noted that "case after case presents itself in which the malady runs its course without implicating the heart, and this even in children who, as a class, show so great a liability to the cardiac accidents of rheumatism." West⁷ criticized the laxity with which the term rheumatic fever had been used in the past and he stated "This is especially true of erythema nodosum, which is still often called rheumatic because of the pains and fever, yet I have never seen erythema nodosum occur in the course of rheumatic fever, nor have I myself observed morbis cordis develop in the course of erythema nodosum, though I know such cases have been described."

Despite the doubts expressed by numerous able clinicians whose combined experience included observations in both children and adults, it is still currently accepted that erythema nodosum per se represents in part at least, one of the rheumatic manifestations. Perhaps the most famous exponent of this view was Stephen Mackenzie^{8a} who presented a paper (1886) based on a study of 108 cases of erythema nodosum. In 17 instances acute and subacute rheumatism were found associated. The criteria for the diagnosis of rheumatic fever rested on the occurrence of combinations of tonsillitis, fever, sour sweats, joint pains, and heart murmurs. However, close scrutiny of this report reveals that in many cases the only signs and symptoms, apart from the eruption itself, were joint pains and fever. Of the 17 instances cited textually, the thirteenth is of particular interest, as post-mortem examination was performed, the patient, a female of 18 years, had suffered from erythema nodosum in the first, second, and third attacks of "acute rheumatism," and finally was observed in the sixth recrudescence of

"rheumatism," accompanied by the eruption for the fourth time, yet necropsy examination disclosed no abnormalities of the heart. It is, of course, realized that this study could not, at that time, have embraced search for myocardial Aschoff bodies or of interstitial valvulitis, both of which may rarely occur in the absence of gross evidence of endocarditis. Nevertheless, it seems improbable that the patient had experienced six attacks of rheumatic fever in the sense in which that disease is understood today. Mackenzie included 17 additional cases of doubtful nature and, on the basis of his statistics, concluded that erythema nodosum per se is a rheumatic manifestation, even in the absence of other signs and symptoms. In 1896 Mackenzie^{8b} presented a comprehensive report based on the study of 125 more cases, which, together with his first group, totaled in all 233 patients. Of the combined series 43 or 19 per cent had suffered from what he called "undoubted articular rheumatism." An additional postmortem examination of a woman 47 years of age again revealed no abnormalities in the heart. These observations at necropsy tend to cast doubt, therefore, on the validity of the criteria used by Mackenzie for the diagnosis of active rheumatic disease. It seems curious that in reporting so large a series of cases, the factor of drug etiology as one of the possible causes of eruptions simulating erythema nodosum was not mentioned.

CLINICAL DATA

In the course of the following presentation, a number of statistical compilations will be cited. The figures are, however, not to be regarded in an arbitrary manner, as individual experiences vary greatly, it will be more instructive to take heed of the general principles involved.

1 *Tonsillitis* Erythema nodosum is accompanied by sore throat in a considerable proportion of cases, the latter being considered by Symes⁹ as the most common prodromal complaint. The average incidence of antecedent angina appears to be about 20 per cent (Bucher,¹⁰ 18 per cent, Hegler,¹¹ 20 per cent, Rolly,¹² 26 per cent). Hegler observed that the eruption succeeded sore throat after an interval of from three to seven days, others claim this period to be as long as 14 days or more (Symes), and it is possible that this symptom may be forgotten by the patient when the skin lesions make their initial appearance. Collis¹³ recorded an instance in which the dermatosis occurred after each of five separate attacks of tonsillitis. I have encountered several examples where this sequence of events was observed on two or more occasions. On the other hand, sore throat may first become manifest during the course of erythema nodosum or even subsequent to it. Skin lesions may also appear in the wake of other varieties of oral infection, such as alveolar periostitis (Arborelius¹⁴).

The incidence of sore throat will depend, in great measure, on the type of material studied. In a dispensary service, where milder instances of the disease are seen, tonsillitis is a prodromal complaint in only a small proportion of patients, roughly in about 15 per cent, when average care is exercised.

in taking a history. In patients with symptoms of sufficient severity to warrant hospitalization, the condition is more common, estimated at from 40 to 60 per cent.

Some observers believe that the occurrence of antecedent sore throat is evidence favoring the rheumatic etiology of the dermatosis. Such evidence per se does not, however, warrant this broad generalization, for it is known that tonsillitis may precede or accompany other affections having no particular relation to rheumatic fever. Moreover, the "rheumatic sore throat" appears to possess no pathognomonic clinical features by which it can be differentiated from ordinary angina. Gueissaz¹⁵ advanced the attractive hypothesis that the antecedent tonsillitis of erythema nodosum may pave the way for the rheumatic agent, but this theory is based on the supposition that joint involvement is necessarily synonymous with rheumatic fever. According to Hegler, there seems to be a parallel relation between the occurrence of sore throat and subsequent joint pains in erythema nodosum, but this association is by no means absolute.

2 Joint Involvement In many instances the diagnosis of rheumatic erythema nodosum has been postulated on the sole basis of articular pains, encountered commonly in the course of erythema nodosum (Hegler, 67 per cent, Mackenzie, 19 per cent). It is likely that articular pains are more frequent than is generally supposed, and that the figure arrived at will depend, to a great extent, on the type of material available for observation.

Patients seen in an ambulatory dispensary service only occasionally complain of articular disturbances. Frequently these are so mild that persistent interrogation is necessary to elicit this information. On the other hand, it may be difficult to distinguish these pains from the local discomfort produced by skin lesions, particularly when the latter are situated about the joints. Redness of skin overlying joint areas appears to be most commonly caused by cutaneous lesions, less frequently by peri-articular involvement, and rarely by intra-articular disease; it may be a clinical feat to determine with accuracy which of these factors is in operation. Fever may be minimal or absent throughout the short period of observation. Such patients are seen once or twice thereafter and then discharged as cured.

On the other hand, cases admitted to the wards of a hospital often present severe concomitant constitutional symptoms. Fever is generally found and may even attain a height of 105° F in exceptional instances. Progressive anemia may be noted occasionally. Usually the patient complains of moderately intense joint pains and while it is difficult to demonstrate definite intra-articular involvement, it is my impression that peri-articular disease was an occasional cause. In most instances the pains are of the nature of arthralgias. In the average case the symptoms are limited to the ankles and knees, but at times the joints of the upper limbs may be affected either simultaneously or subsequently, even in the absence of overlying skin lesions.

In the older literature the arthralgias encountered in erythema nodosum were designated as "rheumatoid" or "pseudo-rheumatic" for the purpose

of differentiating them from true rheumatic polyarthritis (See, Trousseau and others) Of 45 cases of erythema nodosum seen in adults, Hegler¹¹ noted rheumatoid pains in 21 patients (46·7 per cent) Comby,¹⁶ in a study of 172 children exhibiting these skin lesions, encountered 21 instances with joint pains (12·2 per cent), whereas Kuhn,¹⁷ also reporting on the disease in childhood, observed articular discomfort in but 2 out of 22 patients (9·1 per cent) There are many observers, particularly pediatricians, who deny the occurrence of joint manifestations in erythema nodosum Comparison of statistics indicates a higher incidence of "rheumatoid" pains in adults than in children H Koch¹⁸ has recently offered another interpretation of this phenomenon, claiming that there is no articular pain or swelling in association with erythema nodosum, but that the symptoms are produced by periosteal involvement, thus he was able to demonstrate microscopically in one case However, a single instance of periostitis, possibly the result of contiguous spread of the inflammation, does not warrant generalization

The association of "undoubted articular rheumatism" with erythema nodosum was recorded by Mackenzie^{8b} in 43 out of 233 cases (19 per cent) and by Hegler in 20 per cent of 45 cases, these observers were concerned principally with adults In children Comby¹⁶ reported but two instances (1·2 per cent) in a series of 172 examples of the skin disorder Comparison of statistics again reveals a higher incidence of joint involvement in the older age-group The term "undoubted articular rheumatism," when defined precisely, referred to swelling of the articulations, a manifestation considered to indicate true rheumatic articular disease in every case This view, therefore, requires qualification There are, however, occasional descriptions of erythema nodosum accompanied by articular disturbances closely simulating these regarded as characteristic, but not necessarily pathognomonic, of rheumatic fever Thus, cases have been recorded where there was migration of pains from one joint to another (Collis¹³), others in which the skin overlying the articulations was reddened, presumably from intra-articular disease (Patteson¹⁹), and still others in which the joints were exquisitely tender (Coburn²⁰) However, these phenomena are relatively uncommon Symes expressed the point succinctly when he stated that he had never observed in erythema nodosum the intense pain and fear of movement seen in acute articular rheumatism or gout, a statement with which my observations are in general accord I have encountered occasional instances, particularly in adults, where there was an indefinite systematic progression of joint involvement simulating migratory rheumatic polyarthritis At times pitting edema of the skin overlying articulations may be observed, especially in the vicinity of the ankles These cases could usually be differentiated from true rheumatic polyarthritis by the absence of effusion into joints, of characteristic flitting from one part to another, of exquisite tenderness and fear of movement, by the retained ability for active and passive motion when care was exercised, and by the general therapeutic inefficacy of salicylate therapy Broadly considered, these criteria apply in

the differential diagnosis from adult rheumatic fever, though it must be remembered that even in older persons, articular signs and symptoms may be just as atypical as in children. Nevertheless, it seems striking that erythema nodosum in adults rarely presents the features commonly encountered in typical rheumatic polyarthritides of the same age-group. In children, in whom articular symptoms are often atypical or lacking, other criteria must be invoked, particularly those concerned with evidence of cardiac involvement.

3 *Cardiac Disease* (a) *Endocarditis* Many authors (Hegler, Mackenzie, Kuhn, and Symes among others) have recorded the occurrence of transient systolic bruits at the apex or base of the heart in patients with erythema nodosum. Hegler, in particular, observed that occasionally the normal heart sounds may become impure, and that systolic murmurs may appear at the apex of the heart independently of the occurrence of articular pains. However, he recognized that genuine valvular defects, during or after the onset of erythema nodosum, "belonged to the rarities." Zuchholdt,²¹ an adherent of the view that endocarditis is an associated finding, made the significant statement that termination in mitral stenosis was rare. The auscultatory evidence of cardiac bruits, in association with joint pains and, perhaps also, antecedent sore throat has influenced clinicians to classify such cases as rheumatic fever, when the tuberculin test is negative, but this view often lacks substantial proof. The deceptive nature of functional murmurs as revealed by postmortem examination need only be mentioned. Undoubtedly the older literature abounds with instances where accidental bruits were considered as of organic origin. Symes stated that he had never seen cases with persistent systolic murmurs, these transient bruits were, in his opinion, either haemic in type or due to temporary dilatation of the heart. In many instances varying grades of anemia may develop, probably accounting for some of the functional murmurs heard. The minimum evidence required to deduce a relationship between erythema nodosum and rheumatic fever is the demonstration of organically diseased heart, occurring either simultaneously or subsequently. This statement is offered advisedly, as it is realized that the *clinical* evidence for the recognition of cardiac disease may not be apparent at the time of examination. When, however, postmortem study is available, it seems fair to insist on this criterion, the validity of which appears to be gaining ground (Fahr²² and others). No attempt will be made to describe the evidence of recent and old rheumatic involvement of the heart in its various forms, other than to state that there are ample criteria whereby the rheumatic nature of a case may be verified easily on microscopic examination (Gross). But the problem does not end with the demonstration of cardiac involvement, as will be shown in subsequent sections of this article.

From a clinical point of view, Gueissaz¹⁵ reported 300 examples of erythema nodosum in children and adults, with not a single instance of concurrent endocarditis. Gosse,²³ in a series of 100 carefully studied cases in

all age groups, was unable to find any example of endocarditis, and subsequent observation failed to disclose cases with mitral stenosis or other valvular defect Kundratitz,²⁴ Pollak,²⁵ Feer,²⁶ and Kuhn¹⁷ among others were unable to discover a single instance of organically diseased valves in 81, 48, 45, and 22 children respectively with skin lesions of erythema nodosum Of 86 cases of erythema nodosum observed in childhood, Ernberg²⁷ saw but one instance with valvular defect, but even in this isolated example he could not be certain of the relation Comby, in 172 instances of the disorder in children, reported but two examples with coincident "acute articular rheumatism" and "mitral endocarditis," but he furnished no details relative to the precise nature of the valvular defect Of 130 cases of erythema nodosum reported by Landau²⁸ in patients whose ages ranged from between 1 and 14 years, only once (0.8 per cent) was there an antecedent history of rheumatic infection, on the other hand, in 136 instances of rheumatic fever, Landau found a history of erythema nodosum in but four patients, an incidence which he regarded as no greater than that in other childhood disorders I have observed many instances labeled as rheumatic erythema nodosum, owing to the occurrence of sore throat, joint pains, and a systolic bruit at the apex of the heart, but in no instance did the subsequent course disclose evidence of valvular defect, although some of the patients were followed for over five years A distinction may be drawn between two types of cases (1) where erythema nodosum occurs at the beginning of a febrile illness, (2) where erythema nodosum or lesions simulating it appear in a patient known to be afflicted with rheumatic heart disease With regard to the first variety, the point should be stressed that such cases rarely, if ever, develop unequivocal evidence of rheumatic heart disease, when followed over a sufficient period of time The recorded statistics on this phase of the subject, therefore, appear to be at variance with the view that rheumatic fever plays a major, or even a minor part, in the causation of this skin manifestation

(b) Electrocardiographic observations have disclosed but few instances with significant abnormal changes Master and Jaffe,²⁹ on the basis of daily electrocardiograms, concluded that "Cases of erythema nodosum revealed little evidence of myocardial damage and hence the relation to acute rheumatic fever is probably remote" Spink³⁰ observed that in 30 examples of erythema nodosum where serial studies of this type could be pursued, two cases showed evidence of prolongation of the P-R interval and one of myocardial disease In evaluating data of this sort, it seems advisable to stress the points that (1) alterations in the electrocardiogram are not necessarily pathognomonic of rheumatic fever and are to be considered in terms of the entire clinical picture, as there are other diseases where similar changes may be encountered, (2) the criteria relative to prolongation of the P-R interval, particularly in border-line cases, vary with individual observers, this applies especially in the case of children, (3) the value of the fourth lead, as it concerns rheumatic fever, is still uncertain, this point is mentioned

as examples of erythema nodosum may be reported in the future with data bearing on this aspect of the subject, (4) finally, it remains to be noted that erythema nodosum or lesions resembling it may occur coincidentally in the course of undoubted rheumatic fever, this point will be elaborated upon in subsequent sections

(c) The simultaneous occurrence of pericarditis and erythema nodosum is extremely uncommon. In a survey of recent literature, Tachau¹ was unable to find a single instance of this combination. Coombs³¹ has stated that this association is not necessarily diagnostic of rheumatic fever, for, according to this observer, it may occur in erythema nodosum complicated by tuberculous pericarditis and miliary tuberculosis. Pericarditis may also appear as one of the manifestations of bacteremia accompanied by erythema nodosum-like lesions.

4 *Chorea* The association of chorea with erythema nodosum has been noted by a few observers (Garrod,³² Mackenzie, Bass,³³ Claman³⁴). Of 410 cases of chorea, Osler³⁵ found but one instance of this eruption or lesions resembling it. In a series of 100 cases of erythema nodosum, Gosse²³ encountered but a single instance of chorea, this he considered as indicating probable coincidence of diseases. The possibility of bromide or iodide erythema nodosum must be taken into account in cases of chorea where such medication may have been prescribed, as in a case observed by Bass³⁶. Considering the evidence at hand, the association of erythema nodosum with true chorea minor may be regarded as rare.

5 *Subcutaneous Nodules* The concomitant appearance of erythema nodosum and genuine rheumatic subcutaneous nodules is most uncommon. The association of the two manifestations has been reported by Weintraud,³⁷ Cheadle,³⁸ and, more recently, by Claman,³⁴ but it seems interesting to note that in at least the first two cases mentioned, the heart was not found to be involved. This appears curious when one considers the practically invariable occurrence of valvular disease with rheumatic subcutaneous nodules. I know of one example of this so-called combination of disorders, but in this case an erroneous interpretation of the phenomenon was offered, what was described as "rheumatic subcutaneous nodules" represented, in reality the remains of lesions of erythema nodosum which had implicated the panniculus adiposus without marked involvement of the superficial skin. Cognizance must be taken of the point that when the efflorescences of this skin malady are abortive in type or in the process of involution, they may lie subcutaneously, so far as the palpating finger can tell. The possibility of calling them "rheumatic subcutaneous nodules" is not remote, especially when one is influenced by the opinion that erythema nodosum is a rheumatic manifestation. The greatest care must be exercised in describing as rheumatic nodules those lesions occurring subcutaneously at the former sites of an eruption of erythema nodosum, as the latter may leave nodular infiltrations, without redness of the overlying skin, when the panniculus adiposus is involved to

a major extent This phenomenon appears to be more commonly encountered in the case of erythema nodosum of drug origin

6 *Pleurisy* With few exceptions (Wiborg³⁰ and others), implication of the pleurae has been uncommonly encountered in the course of erythema nodosum, except in the Scandinavian countries Of 30 cases of this skin disorder, Wiborg reported eight instances manifesting evidence of pleural involvement, of his entire series, 26 were patients whose ages ranged from between eight and 15 years This high incidence of pleurisy is nowhere duplicated or even approximated, except in reports emanating from Scandinavian countries where tuberculosis appears to be especially common Moreover, these cases have been cited as proof of their tuberculous etiology rather than that of rheumatic fever While symptoms of pleural involvement may occur in the course of rheumatic fever (pneumonia, pulmonary infarction, contiguous spread from pericarditis, hydrothorax, rheumatic pleurisy?), it seems doubtful that this isolated phenomenon can of itself establish the diagnosis of rheumatic disease There are observers who have never encountered this combination of disorders I have met with one such isolated instance exhibiting an unusually protracted course, but am unable to furnish information relative to the outcome In any event, it appears that pleurisy is a relatively uncommon phenomenon in the course of erythema nodosum, except in cases recorded from the Scandinavian countries

At this point it may be pertinent to mention the occurrence of a phenomenon that is foreign to the clinical picture of rheumatic fever, namely, the observation of hilar shadows in roentgen-ray pictures The presence of hilar glands has been variously estimated at from 50 to 90 per cent of cases of erythema nodosum affecting children I have seen several instances of this cutaneous malady in adults who likewise showed pronounced hilar shadows on roentgenologic examination, and it is likely that "hilitis" is more common in adults than has been suspected, this phenomenon being overlooked owing to its asymptomatic nature It is not my purpose to discuss the significance of this manifestation, except to state that its etiology is uncertain as yet Though the tuberculous nature of this phenomenon is accepted by most authorities, there are many lacunae in our knowledge of its nature

7 *Salicylate Therapy* On the basis of the alleged rheumatic etiology of erythema nodosum, salicylate therapy has been, and is still, used widely in this disorder It appears to be clinically established that the pyrexia and joint pains of rheumatic fever usually yield in a striking manner to these drugs, however, similar results may be seen occasionally in other forms of arthritis Gosse stated that salicylates have no influence on the essential course of erythema nodosum Lendon abandoned the use of the drug as it had little effect on the pains and fever curve of erythema nodosum and the experience of Symes appeared to be similar in this regard Whatever therapeutic results have been claimed for this form of therapy must be tempered by the knowledge that this skin disorder is generally of self-

limited course and of short duration. On the other hand, Hegler recorded an instance in which large doses of salicylates were powerless to prevent the appearance of the eruption.

8 *Activity in the Rheumatic Process* In order to determine the relation of an eruption to rheumatic fever, it appears advisable to lay down the following practical postulates: (1) the disease process must be definitely one of rheumatic fever and the evidence must point towards activity in the disorder, to the latter part of this rule, there are some exceptions which will be discussed in another report, (2) the eruption must be related to the rheumatic process in such manner as to eliminate the possibility of coincidence of conditions. Relative to the first point, I have observed two instances of erythema nodosum appearing in patients with inactive rheumatic heart disease of many years' duration. Both were middle-aged women exhibiting signs and symptoms of mild congestive cardiac failure, subsequent observation failed to reveal clinical evidence of rheumatic activity. In one case the eruption had recurred at intervals during the antecedent two years, no attempt was made to prove a probable drug etiology, although it was known that she had been taking potassium iodide during this period. In the other case the dermatosis, morphologically resembling banal erythema nodosum in all particulars, was probably also caused by the intake of medication, as she had been using drugs to "relieve the nerves." It appears that the eruptions were in no wise related to the rheumatic process since in both instances, quite apart from their probable drug origin, they occurred in the absence of definite evidence of rheumatic activity. Had these patients come to post-mortem examination, chronic valvular defects attributable to rheumatic disease would have been found in all probability, demonstrating the point that the observation of rheumatic heart disease post mortem in a patient previously afflicted with an eruption resembling erythema nodosum does not necessarily imply a relation between the two conditions.

In addition, I have encountered several instances of erythema nodosum occurring in association with rheumatoid arthritis, non-gonorrheal in type. These cases were characterized by the absence of evidence of rheumatic heart disease. Such examples do not necessarily warrant the belief that rheumatoid arthritis and rheumatic fever are conditions related to one another or caused by the same etiologic factor.

9 *Comparison with the Known Rheumatic Eruptions* Although ordinary erythema nodosum may be characterized by the appearance of a few successive crops of lesions and by subsequent relapses of the condition in occasional cases, it appears to differ clinically from the known rheumatic erythemas of the popular, marginated or flat circinate varieties (Keil). The latter exhibit clinical attributes that remind the observer of the essential characteristics of the rheumatic process. They appear suddenly, their tenure of life is transient, lesions coming and going within a period of hours, occasionally one or more days, there is definite predilection for the trunk, they spread rapidly at their peripheries and have a marked tendency to form

configurations and bizarre shapes, there are usually many crops of lesions and, in occasional instances, they exemplify the chronicity of the rheumatic process by appearing at sporadic intervals over periods of months, and, rarely, even of years, there is generally associated undoubted evidence of heart disease, if not simultaneously, at least subsequently, and they are often accompanied by such rheumatic stigmata as transient subcutaneous nodules and chorea. The clinical course of an individual lesion is far more rapid and dynamic than in the case of erythema nodosum. On the other hand, the latter disorder, occurring at the inception of a febrile illness and being followed by undoubted evidence of cardiac involvement, is exceedingly uncommon.

10 Pathologic Features The absence of characteristic Aschoff bodies in erythema nodosum cannot of itself be used as an argument against its rheumatic origin, as this seems to be likewise true of the microscopic anatomy of the known rheumatic erythemas, concerning which, however, more study is necessary. Some observers are drawing etiologic conclusions on the basis of similarities in histologic alterations to the lesions described by Klinge.⁴¹ For example, Coburn⁴⁰ reported the case of a young woman who had erythema nodosum followed by polyarthritis. On the basis of the joint symptoms and the microscopic findings in sections of skin, he concluded that the eruption was of rheumatic origin. Histologic study disclosed vascular changes characterized by "swelling of endothelial cells which appeared frayed out into the lumen" and "escape of erythrocytes through the wall of the vessel, causing hemorrhage into the surrounding tissues. Throughout the connective tissue and fat, there were scattered foci of infiltration by polymorphonuclear leukocytes. There were also areas of swelling of the fixed tissue cells and an edematous appearance of the tissue itself. In one or two of these areas, multinucleated cells were seen." While swelling of the collagen bundles of the skin as well as vascular changes accompanied by intense edema of the pareties may present gross similarities to the type of lesion described by Klinge, it seems fair to note that such pathologic alterations have not been demonstrated beyond peradventure to be necessarily pathognomonic of rheumatic fever. The histologic description recorded by Coburn corresponds with that observed in banal erythema nodosum (Symes), even to the presence of giant cells which apparently represent a reaction to foreign bodies (particularly fat products) formed in the panniculus adiposus. Similar pathologic alterations may be encountered in cases of erythema nodosum where there is no definite evidence of rheumatic fever. This is one instance where clinical study seems to yield data of greater importance than that furnished by the pathologic approach.

CONSIDERATIONS ON THE MORPHOLOGY OF ERYTHEMA NODOSUM

The typical morphologic features of erythema nodosum need not be described, as the classical features are familiar to all. However, there are many atypical variants, the recognition of which is often difficult and the

status of which is generally uncertain. The ordinary evolution in the manner of a bruise (*dermatitis contusiformis*) is occasionally lacking or inconspicuous, the lesions presenting a delicate rosy hue or a faint purplish blush. Rarely, the eruption may be disposed unilaterally (diagnosed commonly as osteomyelitis, erysipelas, or septicemia) or a few efflorescences may appear on the contralateral limb either simultaneously or subsequently. While the lower extremities are the favored sites, it is not uncommon to find crops of lesions, usually of the small papular type, scattered on the upper extremities, notably about the elbows and wrists. In atypical situations, as on the face, lesions frequently reveal marked exudative qualities simulating the erythematovesicular type of erythema multiforme exudativum. In a considerable percentage of cases, eye lesions diagnosed as phlyctenular conjunctivitis or as episcleritis have been encountered, that these manifestations represent either rheumatic or tuberculous changes seems to be unproved as yet, though many investigators are in favor of the tuberculous etiology. Other observers have recorded the occurrence of oral mucous membrane lesions, an extremely rare manifestation with uncertain status. Lendon described splinter hemorrhages under the nails (Verco's sign) as part of the clinical picture of erythema nodosum. However, this phenomenon has not been encountered by other observers as well as myself and its status is also considered *sub judice*, painful subungual splinter hemorrhages are most commonly met with in subacute bacterial endocarditis, while, more rarely, massive extravasations of blood into the nail beds may be seen in "systemic" lupus erythematosus. The pseudo-fluctuant character of many lesions of erythema nodosum is probably caused by liquefaction of the neighboring subcutaneous fat when the inflammatory process affects the panniculus adiposus, but spontaneous resolution occurs without resultant necrosis or ulceration of the overlying skin. When an eruption is composed of elements that break down, there is reason to doubt the validity of the original diagnosis of erythema nodosum.

Galloway⁴² stated that he had observed two types of lesions in this skin disorder, the papular and large nodular varieties. However, he made no attempt to differentiate them etiologically, nor did he cite illustrative cases. In a more recent publication, Collis⁴³ has proposed separation into the following two morphologic and etiologic categories, first, the large nodular flouid type attributed to rheumatic fever or, more generally speaking, to streptococcal infection, second, the small nodular (papular?) form associated with tuberculosis. Relative to the rheumatic variety, the evidence presented, thus far, to adduce a relationship appears to be inconclusive. Although the classification advocated by Collis is not entirely acceptable on morphologic grounds, it has the merit of stimulating interest in clinical minutiae as a means of etiologic differentiation.

It is not my purpose to discuss fully the differential diagnosis from a strict dermatologic point of view but rather to point out certain principles illustrating pitfalls in the classification of eruptions simulating erythema

nodosum In making this attempt the account will necessarily have to be incomplete, as the principal design will be to draw on personal observations, completing them with the opinions of other investigators. It will be shown that much of what has been quoted in the literature as *erythema nodosum* belongs in reality to another category of disease.

(a) *Erythema Multiforme Exudativum* This disorder, originally described by Hebra, presents a series of typical clinical phenomena, and in its ordinary form is easily differentiated from *erythema nodosum*. Like the latter disease, it has also been attributed to "rheumatism" but the evidence speaks clearly against this view (Tachau, Keil). The dermatosis may be associated with lesions on the lower extremities where, owing to the influence of location, they are apt to be somewhat nodular, show a cyanotic hue, and reveal tenderness on palpation (Veiel⁴³). This variation has been attributed, in large measure, to the superimposition of an element of circulatory stasis and it is this type that is often described as *erythema multiforme exudativum* combined with *erythema nodosum*. There are, however, occasional border-line instances, notably when *erythema nodosum* takes on exudative qualities, where differential diagnosis is most delicate. Despite the latter occurrence, it would be unwise to regard the febrile forms of these disorders as identical, without further study of so-called transitional instances. In its classical form, *erythema multiforme exudativum*, a well-characterized disease, differs radically in the location, morphology, and clinical course of its skin and mucous membrane manifestations.

(b) *Erythema Multiforme of Rheumatic Origin* Here we enter on a somewhat delicate subject. Many years ago Garrod³² recognized the influence of the factor of location on the morphology of rheumatic dermatoses, when he described papular and margined eruptions on the trunk in association with nodular painful lesions on the lower limbs. Josias⁴⁴ mentioned a similar observation. I have encountered an example of the phenomenon displayed by isolated lesions situated on the inferior extremities in a case of active rheumatic heart disease, to have labeled this eruption as *erythema nodosum* would have been stretching the point far beyond the criteria set down for the diagnosis of the latter disorder. Such dermatoses are always labeled *erythema nodosum* hesitatingly, though a review of clinical charts many years later may not lead to recognition of the uncertainties of the original diagnosis. In any event, the occurrence of small, somewhat painful lesions in the course of rheumatic fever does not necessarily mean that the eruption in question was that of *erythema nodosum*. The principle that skin lesions situated on the lower limbs may acquire attributes simulating *erythema nodosum* is also borne out by study of other dermatoses.

(c) *Chronic Bacteremia* Isolated skin lesions of painful and nodular character may be encountered occasionally in the course of various forms of bacteremia in the acute as well as the more chronic types, but notably in the latter variety (subacute bacterial endocarditis, chronic meningococcemia,

gonococcemia, enterococcemia, etc.) Because of their physical attributes, these eruptions are often classed as examples of atypical erythema nodosum, unlike the latter disorder, the lesions are generally discrete and few in number, are situated at other sites of predilection (especially the upper limbs), do not show the characteristic gamut of color changes, and undergo involution in a short time, usually measured in hours to one or two days. In their physical characteristics, they are strikingly analogous to the Osler Node a term generally applied to the painful lesions observed on the finger tips, toes and other parts in subacute bacterial endocarditis. I have seen cases of chronic bacteremia diagnosed as rheumatic fever because of the presence of skin lesions, fever, polyarthralgias, functional or organic heart murmurs, and even prolongation of the P-R interval in electrocardiograms. Blood culture studies are usually of prime aid in establishing a correct opinion, sometimes the finding of the causative organism in sections of skin may provide the first clue. The difficulties confronting the clinician in the face of nodular painful eruptions accompanied by a clinical picture resembling rheumatic fever are therefore apparent. These skin lesions are not representative of true erythema nodosum and should not be labeled with this name, otherwise, the subject will become necessarily complicated by the introduction of miscellaneous dermatoses.

(d) *Tuberculides* There is a more acute variety of erythema induratum revealing transitions to papulo-necrotic tuberculides and resembling erythema nodosum. Of this variant I have encountered three examples, characterized by the occurrence of cervical lymph node tuberculosis, typical papulo-necrotic lesions about the elbows, and painful, purplish red, nodular efflorescences on the lower limbs. The latter simulated ordinary erythema nodosum, the resemblance being further promoted by the failure to ulcerate and the assumption of an intense purple hue in the course of gradual involution. They differed, however, in their longer duration, in their association with typical lesions of papulo-necrotic tuberculides (some of which failed to show the characteristic central necrosis), and in the presence of chronic active tuberculosis of the lymph gland variety. It is possible that this type may be more properly labeled as papulo-necrotic tuberculide with atypical lesions on the lower extremities, the physical attributes of the latter being markedly modified by location.

I have also encountered several examples of non-ulcerating erythema induratum (Bazin type) in which the dermatoses were diagnosed as erythema nodosum owing to the painful nature of some of the lesions. It is possible that cases of this type may be given the title of chronic erythema nodosum. It is my belief, however, that erythema nodosum is chronic only in the sense that many relapses of the eruption may occur or, in the absence of recurrent cutaneous manifestations, that constitutional symptoms, such as fever, continue unabated over a relatively long time, the appearance of skin lesions for many weeks is not necessarily an indication of longevity.

in the individual efflorescences, but rather is ascribable to the superimposition of fresh crops on fading lesions

(e) *Syphilides* It appears from the accounts of several observers, notably that of Hoffmann,⁴¹ that there are instances of secondary syphilides resembling ordinary erythema nodosum. The precise status of this rare group is still unsettled, some of the cases seem to be instances of secondary syphilides with specific involvement of blood vessels of the lower limbs and elsewhere, resulting in skin lesions apparently indistinguishable from erythema nodosum, others may be examples of coincidental banal erythema nodosum, still others, of drug eruptions particularly those caused by iodides or bromides, and, finally, some cases may represent instances of gummas that have resorbed completely without concomitant ulceration. The importance of this group of cases, as described by Hoffmann, lies in (1) the possible confusion with banal erythema nodosum, (2) the similarities in clinical picture to that of rheumatic fever, since in several of the recorded examples "rheumatic pains" occurred (syphilitic periostitis?) and in occasional instances the joints were said to have been swollen and red. Since the publication of Hoffmann's comprehensive report of 11 instances of secondary syphilides resembling erythema nodosum, there have been but few additions to the casuistic literature and these, for the most part, doubtful in nature. How confused the subject has become is indicated by the citation (Spink³⁰) of Stillians and Seneat's⁴² case as one of erythema nodosum syphiliticum, this case presentation provoked considerable debate relative to the status of the eruption and it seems interesting that the subsequent course revealed ulceration of the nodules in the manner of gummas. This instance cannot, therefore, be classified as an example of erythema nodosum. The entire subject of erythema nodosum syphiliticum is in need of clarification. No convincing proof has been recorded as yet that ordinary erythema nodosum may be a syphilitic manifestation, it is, however, granted that secondary and tertiary syphilitic skin lesions may occasionally present close clinical similarities to ordinary erythema nodosum.

(f) *Skin Lesions of Ulcerative Colitis* The statement that erythema nodosum occurs in the course of chronic ulcerative colitis (Spink) has been based on the statistics furnished by Baigen⁴³ who in 693 cases of this disease, found 17 instances exhibiting skin lesions, particular mention having been made of erythema nodosum, no detailed case reports are, however, available so far as I was able to ascertain. From my own comparatively meager observations, it appears that this chronic disorder may be complicated occasionally by eruptions composed of nodular, painful, bluish red lesions, often called erythema nodosum at first sight, yet, further observation has revealed significant differences. In one striking instance, for example, the lesions which were situated on the lower limbs, and which at first seemed to be those of ordinary erythema nodosum, became filled with fluctuant bags of pus and then proceeded to break down. In another case efflorescences, similarly located, ulcerated rapidly. In still another example, there appeared

crops of painful, dull red papules over the upper and lower limbs, the dermatosis, however, lacking the ordinary physical attributes of erythema nodosum. The resemblance to erythema nodosum may be further promoted by the occurrence of joint symptoms which may occur in the course of chronic ulcerative colitis itself. Other observers have recorded analogous instances which may be conveniently divided into two arbitrary groups with transitions. (1) ulcerative lesions on the lower limbs, commonly termed pyoderma gangrenosum (Brunsting, Goeckerman, and O'Leary,⁴⁸ and Cohen⁵⁰ among others), larger areas of necrosis may also occur on other parts of the body, such as the trunk, (2) eruptions composed of efflorescences that early in the course may simulate erythema nodosum strikingly, but where subsequent observations reveal either spontaneous breaking down of lesions (Brooke⁴⁹) or the formation of subcutaneous abscesses (Jones⁵¹). While the latter group may at first give rise to the clinical impression of ordinary erythema nodosum, it is apparent that the resemblances are superficial and occur only in the early course of the eruption. In studying the cutaneous manifestations of a disease like chronic ulcerative colitis which has experienced the gamut of medicinal therapy, it seems necessary to eliminate the possibility of drug etiology in every case of the disease.

(g) *Drug Eruptions* This leads us into one of the most interesting and difficult phases of the problem, a more detailed consideration of which seems advisable in view of the high incidence of nodular painful eruptions of drug etiology.

It has been stated by Tachau¹ that nodular erythemas caused by drugs are distinguishable from ordinary erythema nodosum by virtue of the following features, their location may be atypical, the nodules are fewer in number and reveal tendency to necrosis, characteristic color changes do not appear in their further evolution, constitutional symptoms are lacking, and, finally, the eruption disappears when the suspected drug is stopped. However, these differential points do not hold for all cases, as there are many exceptions to the above stated rules. It is common knowledge, for example, that various medications may give rise to lesions that may simulate ordinary erythema nodosum in every morphologic detail. The problem becomes further complicated when drugs are administered for the alleviation of constitutional symptoms such as fever and joint pains of various causes. However in the average case absence of constitutional symptoms may be regarded as favoring drug etiology but the latter should be verified by history of ingestion of the suspected medication, suitable laboratory tests (for example, urine examination for detection of bromides etc.), and by other cutaneous evidence, such as the observation of a pustular eruption appearing simultaneously (iodides, bromides, etc.). In several instances of "halogen" erythema nodosum I have observed deep subcutaneous nodules which did not directly affect or discolor the overlying skin, substantiating Schidach's³ observations on iodide (nodose) eruptions, this phenomenon

is also encountered occasionally in idiopathic erythema nodosum, for reasons which have already been detailed

Several difficulties may arise in determining the etiology of drug eruption simulating ordinary erythema nodosum. First, the history of ingestion of medication may be inadequate, second, laboratory procedures may be required to demonstrate the suspected drug, third, the patient may refuse to submit to therapeutic tests for purposes of reproducing the lesions *ex juvantibus*, fourth the absence of constitutional symptoms may not necessarily indicate a drug etiology as there are instances of banal erythema nodosum characterized by minimal or insignificant systemic reactions. It seems advisable to discuss these points which are commonly met with in dermatologic practice and which are sources of great difficulty. Appreciation of these difficulties is essential to the understanding of the problem as it relates to rheumatic fever. Dreschfeld⁵² was among the first to suggest the possibility that lesions of erythema nodosum appearing in the course of rheumatic fever might be due to the ingestion of salicylates as he had personally observed this occurrence. Hegler recorded a case of rheumatic fever in which sodium salicylate produced a dermatosis simulating banal erythema nodosum, it differed, however, in the attendant pruritus and lack of color changes in its further evolution. Coburn described an instance of rheumatic erythema nodosum but the clinical attributes, such as itching and overlying vesicles, warrant suspicion of possible drug etiology, a dermatosis exhibiting these characteristics can hardly be classed as a typical example of erythema nodosum. In addition to salicylates, there are other drugs capable of producing skin lesions simulating banal erythema nodosum, among these may be mentioned quinine compounds, iodides, bromides, pyrimidon, etc. It will be recalled, as a point of historical interest, that quinine and, in particular, potassium iodide were widely used in the treatment of rheumatic fever during the middle of the nineteenth century. The frequency with which iodides, for example, are capable of causing nodose painful eruptions is well known today, but apparently older observers were not aware of this point or did not take it sufficiently into account. On the other hand, there is a great tendency to suspect drug eruption merely because medication has been administered, leading inevitably to errors in diagnosis. Each case must, therefore, be individualized and, whenever feasible, an attempt should be made to prove the nature of the dermatosis by *controlled* therapeutic tests which, in final analysis, furnish the most decisive proof.

However, this procedure carries with it the possibilities of certain errors which should be recognized. (1) a given single dose of a drug may not reproduce the dermatosis *ex juvantibus*, in other words, eruptions are not always caused by marked hypersensitivity to a small quantity of medication, rather, a definite concentration of substance must be reached in the tissues before skin lesions occur. It is common knowledge, for example, that patients may take iodides or bromides for a long time before a dermatosis appears. I have also observed a case of "fixed" eruption caused by venereal,

where 10 grains of the drug reproduced the eruption, whereas 5 grains were without effect. The occasional statement found in the literature with respect to a latent period following the onset of a drug dermatosis, during which period the suspected medication is incapable of reproducing the skin lesions, needs substantiation in the light of the foregoing remarks. (2) It is necessary in trying the tests to eliminate the possibility of spontaneous relapses of the cutaneous manifestations, an especially common occurrence in erythema nodosum. It does not seem, however, from recent experimental work, that this factor has been sufficiently appreciated, and, unless one is exceedingly cautious, etiologic conclusions based on "therapeutic fallacies" may be drawn. Nonspecific effects also need to be recognized and evaluated.

It will be seen, therefore, from the foregoing comments, how many difficulties may present themselves in the diagnosis of an eruption as true erythema nodosum and how much care is necessary if one wishes to attack this problem in as scientific a manner as the subject permits.

SUMMARY AND CONCLUSIONS

The hypothesis that erythema nodosum represents one of the rheumatic series had its roots in the original communications by S. Mackenzie who was instrumental in popularizing it. This was accomplished during an era when the term rheumatic disease did not enjoy the precise meaning which it now possesses, the criteria employed by Mackenzie were, therefore, vague and much too elastic, a circumstance recognized by many of his contemporaries whose dissenting opinions were cited. Mackenzie's views are, however, still widespread among practitioners and, indeed, his statistical evidence is still quoted as corroborative of the hypothesis. When the diagnosis of rheumatic erythema nodosum is postulated, there is automatically conveyed to the mind of the observer the potentialities of subsequent serious cardiac disease, and it is for this reason that the subject assumes an importance far beyond the theoretical implications.

A number of recent investigators, recognizing that many cases reveal no evidence of rheumatic fever at any time, have adopted the eclectic point of view that a certain variable percentage of erythema nodosum is of rheumatic origin. Too often such beliefs are based on impression and no serious effort made to ascertain the fate of such patients. Complicating the problem has been the attempt of some observers to separate the disease as seen in children from that in adults, a point of view that does not seem to be corroborated by study of the disorder in all age-groups. When one analyzes the characteristics of the genuine rheumatic dermatoses (papular, marginated, and flat circinate erythemas of rheumatic fever), there appears reason to doubt that erythema nodosum belongs in the same category. As argument by analogy alone may prove treacherous, it was decided to study the entire subject in a critical manner.

At the outset, it must be emphasized that a condition as common as is rheumatic heart disease may be associated sometimes with erythema no-

dosum appearing as a coincidental and unrelated affection. It is probable that if observers were to look back upon their clinical experience, they would recall an occasional case of this type, where the occurrence of skin lesions had no appreciable effect on the heart disorder clinically, where the eruption resolved in a short time and the patient recovered within a correspondingly brief period without any mishap. In the text there were noted, also, two examples of coincidental erythema nodosum, probably of drug origin, appearing in patients afflicted with chronic inactive rheumatic heart disease, accompanied by mild congestive failure apparently of mechanical nature. What, on the other hand, is to be expected in persons who have never suffered from any of the various rheumatic stigmata, and who present, for the first time, the cutaneous manifestations of erythema nodosum at the inception of a febrile illness, accompanied by joint symptoms and other phenomena? Do these patients develop undoubted evidence of rheumatic heart disease?

The relation of such instances to rheumatic fever was analyzed in terms of the criteria set down for the diagnosis of the latter disease (sore throat, joint involvement, cardiac disease, chorea, subcutaneous nodules, pleurisy, salicylate therapy, active vs inactive rheumatic disease, comparison with known rheumatic erythemas, and the pathologic features). The data recorded seemed to indicate that this alleged relationship rested on tenuous grounds, in many instances it was apparently not realized that the two disorders may present similar but not necessarily identical or superimposable features, resemblances in clinical picture do not connote absolutely alliance between such conditions. It was further noted that many eruptions, frequently quoted in the literature as true erythema nodosum, were in all probability manifestations of another category of disease. This point was illustrated by brief citation of disorders confounded with erythema nodosum as seen within my own observations (erythema multiforme exudativum, erythema multiforme of rheumatic fever in its papular and margined forms, skin lesions encountered in acute and especially in chronic forms of bacteremia, tuberculides of the papulo-necrotic or erythema induratum types, syphilides, cutaneous manifestations of chronic ulcerative colitis, and, most important of all, the nodular, painful eruptions of drug origin). Chief emphasis was placed on the principles illustrating pitfalls in diagnosis, rather than on a close dermatologic consideration of morphologic minutiae. It becomes apparent, in studying a problem of this sort, that the internist cannot rely solely upon his own knowledge of cutaneous manifestations, that reports in the literature must be evaluated with a critical eye, and that studies based on perusal of charts, while valuable and instructive, take second place to personal observation. Too often valuable details relative to eruptions are not recorded or a diagnosis of erythema nodosum may be made diffidently in the hope of subsequent confirmation which may not be forthcoming but which is not apparent to the person reviewing the chart at a later date.

The relation of erythema nodosum to rheumatic fever is, therefore, a problem which should be investigated anew. Cases of this type must be studied over long periods of time in order to eliminate with certainty the possibility of clinically unrecognizable rheumatic heart disease. Every method of approach must be utilized, but the limitations of the various procedures must also be recognized. In patients with inactive rheumatic heart disease, erythema nodosum or lesions resembling it, may occur (*a*) coincidentally, (*b*) as a drug eruption, (*c*) as evidence of rheumatic activity, (*d*) under the guise of an erroneous diagnosis. In persons showing undoubted evidence of active rheumatic heart disease (rheumatic fever), the skin lesions may appear (*a*) fortuitously, (*b*) as a drug eruption, (*c*) as a genuine manifestation of rheumatic origin, (*d*) as part of the nodose lesions seen in rheumatic erythemas, (*e*) as a wrong diagnosis. With regard to true erythema nodosum, it would seem advisable to study the disorder under two heads: (1) in its ordinary primary form, where the lesions appear at the inception of disease without previous evidence of rheumatic fever, (2) where the eruption occurs in a patient who is already known to be afflicted with rheumatic heart disease or has had stigmata of rheumatic fever. My own observations do not appear to substantiate the hypothesis that erythema nodosum is of rheumatic origin, even when preceded by sore throat and followed by joint manifestations. It will not do to label cases of erythema nodosum as tuberculous when the tuberculin test is positive and rheumatic when the reaction is negative.

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THE RELATION OF FUNGUS INFECTION OF GRAIN CROPS TO VASOMOTOR DISTURBANCES IN MAN

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THE relationship of diseases of plants to human health has not received the detailed consideration which it deserves. Although botanists and agriculturists have made intensive studies of plant pathology, there has been no systematic effort to correlate plant disease with human pathology. On perusing the literature with a historical perspective it is interesting to note that the ancients ascribed disease conditions to contaminated cereal crops. Thus Galen refers to the "morbus cerealis," a disease due to eating spoiled cereal. There are also on record epidemics from eating bread made of rye infected with the fungus, *Claviceps purpurea*.¹

Robertson and Ashby² have reported on the symptoms of ergotism found among the Jewish people of Manchester as the result of eating rye bread. The symptoms complained of were coldness in the extremities, numbness and lack of sensation in the fingers, formication, headache, gastric disturbances, shooting pains, twitchings in the limbs, and staggering gait. None of the symptoms were observed among those of the Jewish population who ate white bread. The rye grain examined at Manchester showed an incidence of 1 per cent infected with fungus.

Although the occurrence of epidemics of ergotism is a well known medical fact the widespread infestation of our cereal crops with *Claviceps purpurea*, *Ustilago zeae*, *Fusarium moniliforme* and other grain fungi has been rather overlooked or neglected as a fact of medical importance. *Claviceps purpurea*, the ergot fungus, occurs commonly on rye (*Secale*), and many other species of grass such as wheat grass, wild ryes, Kentucky blue grass, Canada blue grass, red-top, timothy grass, and occasionally wheat. The mycelium of the ergot fungus attacks the ovary of the plant while it is in bloom. The fungus consumes the ovary and replaces it with the ergot which consists of a dense mass of fungoid interwoven mycelium, a sclerotium (figure 1). Cattle fed ergotised grain or grass become emaciated and rough-haired. There is a disturbance in the circulation through the extremities, and gangrene of parts of the tail, ears, and hoofs may occur, as well as abortion.

After having published my preliminary report³ on the etiologic relationship of these grain infestations to vasomotor disturbances such as erythromelalgia, Raynaud's disease, Buerger's disease, Schultz's acro-paresthesia, acrodynia, and hypertension it was called to my attention that J. Kaunitz⁴ in 1930 had contributed a report on the pathologic similarity of thrombo-angitis obliterans and endemic ergotism. His is the first report that I have

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read which attempts to establish the theory that ergotism of a chronic endemic type is responsible for Buerger's disease and related vasomotor disturbances. He notes that the ergot fungus attacks most of the grains and grasses and is present in most portions of the globe. It has been reported in every continent including Australia and New Zealand. Considering the amount of ergot-infected rye bread consumed, Kaunitz is surprised that cases of endemic ergotism are so rarely reported. He further states that it may well be that such conditions as thromboangitis obliterans, Raynaud's



FIG 1 Sclerotium of ergot fungus

disease, as well as other vasomotor and trophic disturbances have been overlooked as possible sequelae to ergot poisoning. This may be because of the mildness of the original intoxication and the insidious onset of the vascular changes. Kaunitz further notes that both thromboangitis obliterans and gangrenous ergotism have a preference for the male sex.

Another aspect of ergotism has been reported by Mellanby⁵ who has demonstrated a very important fact with regard to diet and ergot toxin. On the basis of experimental studies he concluded that food rich in vitamin

A prevents the neurotoxic effects of ergot toxin, while a deficiency in vitamin A increases the degenerative effect of this poison. Furthermore, the addition of cereals and cereal embryo aggravated the degenerative changes induced by the ergot poison. Mellanby demonstrated experimentally that ergot could be consumed with impunity as long as the diet was rich in vitamin A and carotene. This fact is of decided clinical and therapeutic significance.

In the course of the present work I have examined samples of commer-

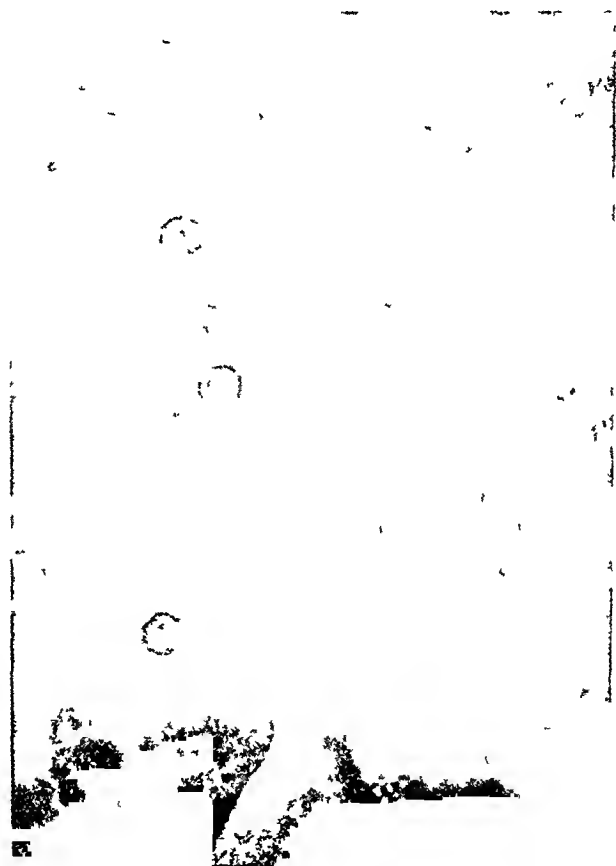


FIG 2 Conidiospores of ergot parasite in commercial rye flour

cial rye flour and pumpernickel bread (whole rye much used by our immigrant population, particularly Slavs) and have been able to demonstrate the conidiospores of the ergot parasite (figure 2). I have also examined corn meal bought in the retail market and have found the spores of *Ustilago zae-mays* (figure 3). Corn is very frequently diseased (figure 4). Among the most common types of corn infestation are the smut fungi, *Ustilago zae* (Koehler⁶). The outstanding characteristic of all the grain smuts is that they nearly always destroy the head or grain of the wheat, rye, barley, corn or oats affected. There are more than 600 species of these

grain parasites recognized, of which 205 are found in the United States. It is estimated by F. L. Stevens and J. B. Hall⁷ that 100,000,000 bushels of grain are affected annually by the development of smut on corn, wheat, oats, rye, and barley. The common corn smut develops on any part of the corn plant but is much more conspicuous on the ears and tassels.

Intoxication occurring in children with all the symptoms of acrodynia has been reported by E. Mayerhofer⁸. In the spring of 1929 he observed two children from the region of Zagreb who presented all the manifestations



FIG 3 Spores of *Ustilago zeae-mays* from cornmeal

of ergotism or acrodynia and who had been fed on contaminated corn. A large content of *Ustilago zeae* spores was found in the corn flour. The intoxication had the pharmacologic and toxic characteristics of ergotism. Mayerhofer has expressed himself as seeing a causal relation between corn smut and acrodynia.

I have isolated *ustilago* spores from commercial corn meal and cultured them on sterilized corn meal media. After a heavy growth was obtained it was extracted with acid alcohol. The resulting product when injected into

an adult rooster caused a blackening of part of the comb, thus demonstrating the ergot effect and the vascular toxicity of the *ustilago* fungus. Sollmann⁹ in his pharmacology notes that corn smut, or *Ustilago zeae*, has a mild ergot action and is frequently used to induce abortion among Southern negroes. A. Marie¹⁰ made extracts of diseased corn and found that it had the properties of ergot.

The chemistry of ergot has been the subject of numerous thorough investigations. Various substances such as amines and alkaloids have been extracted. Dale¹¹ found that the action of ergot was due to the presence of

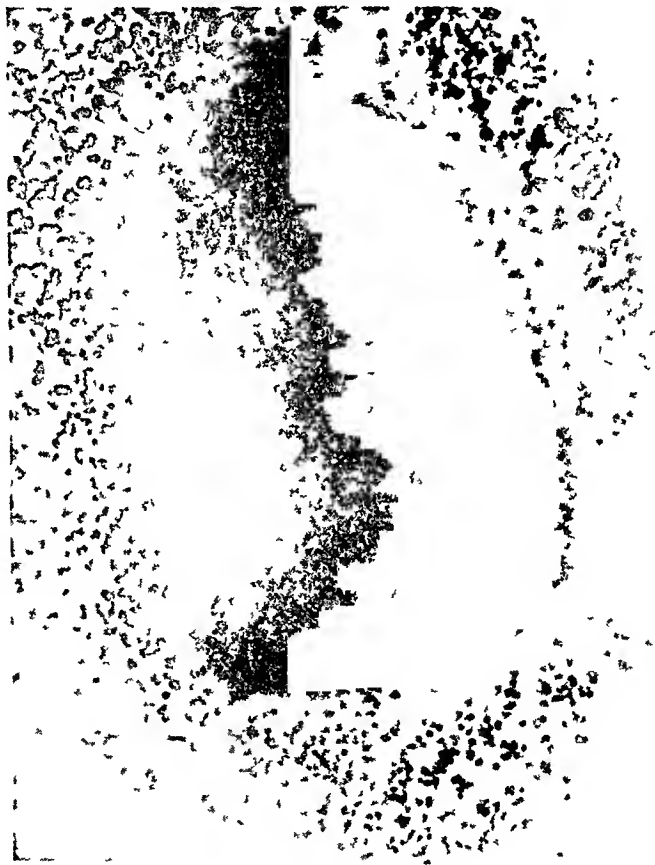


FIG. 4. Incubated corn kernel with *ustilago* fungi growing

ergotoxine, tyramine, and ergamine. More recently Stoll¹² has isolated a crystalline alkaloid, ergotamine tartrate ($C_{22}H_{32}N_2O_6$), which is a chemically pure alkaloid and which has marked potency. It is a pharmacologic antagonist to adrenalin and inhibits the sympathetic nerve endings. It lowers the basal metabolism, causes a diminution in heat production and has a marked action on the uterine musculature. In a dilution of 1-2,000,000, it acts on the guinea-pig uterus and is thought to be the specific alkaloid of ergot. Human beings have been found to be more sensitive to its effects than animals.

I studied the effect of ergotamine tartrate on the white rat. A group of six young white rats were used for the ergotamine experiments and four were held as controls. A solution of two and one-half mg of ergotamine tartrate was injected subcutaneously twice weekly for two months. The drug was also administered daily in the drinking water in the proportion of 0.001 gm to 8 ounces of water. Early in the experiment there was noted a pronounced cyanosis of the tip of the tail in all of the six experimental rats. A dry gangrene of the tail developed in two rats after the first month. The experimental animals seemed quieter than the controls. One, however,



FIG 5 Normal artery of rat's tail

developed symptoms of excitation, ran about the cage, made unusual noises, and acted in a strange manner. After two months all of the animals were chloroformed and autopsied. No noteworthy abnormalities were found on the gross examination. On histologic study the tail arteries of the experimental rats were found to be very markedly constricted so that almost no lumen was apparent (figures 5 and 6). No inflammatory changes were observed.

The various theories proposed at present for the explanation of acrodynia do not seem to be satisfying or conclusive. Feer¹³ has suggested that

the condition is a neurosis of the vegetative nervous system. This is considered plausible by many. Others, on the contrary, ascribe it to some unknown virus infection or even to a deficiency of vitamins. The pathologic findings in the few cases studied have been rather puzzling and unsatisfactory. Most of the attention has been centered on the state of the nervous system with very dubious results.

In view of the conflicting theories on the etiology of acrodynia, the theory that it is due to grain fungus intoxication is brought up for consideration on the basis of the above clinical and experimental data.



FIG 6 Constriction of artery after ergotamine

CONCLUSIONS

1 Our common cereals are frequently subject to fungus infection, particularly *Ustilago* (smut) and *Claviceps purpurea* (ergot).

2 It is suggested that the ingestion of such food over a period of years may produce a chronic intoxication by the contained ergot alkaloids and amines which may be the cause of certain vasomotor disturbances such as acrodynia, Buerger's disease, erythromelalgia, Raynaud's disease, and acroparesthesia.

3 It seems advisable that serious attention be given to the problem of reducing these fungus infections of our common cereals by modern chemical treatment of infected seed and by improved milling methods

4 Plant pathology is of considerable significance in relation to human health and should be systematically studied from this point of view

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CASE REPORTS

BRADYCARDIA IN APPENDICITIS, REPORT OF A CASE¹

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THE occurrence of bradycardia in a patient manifesting acute abdominal symptoms which proved to be due to a gangrenous appendix prompted us to investigate this subject. It is interesting to note that in *The Journal of the American Medical Association* of December 1906, Maurice Kahn¹ directed attention to the presence of bradycardia in appendicitis. He stated that "in the last six cases of gangrenous appendicitis in which this symptom was evinced, the diagnosis of the gangrenous state was made before operation, based on the bradycardia alone. So it would appear from this that given a case presenting other unmistakable signs of appendicitis with a subnormal pulse, the tentative diagnosis of gangrene, with some reason, may be maintained."

Since the appearance of Kahn's original article several French and German authors have added other cases of similar nature to the literature. Von Bokay² in 1908 cited 10 cases of bradycardia in appendicitis in children. Although Kahn believed that the bradycardia in appendicitis was due to the absorption of ptomaines which acted on the cardiac centers or ganglia, Bokay believed the mechanism to be due to vagal stimulation. Broca³ reported an instance of cardiac arrhythmia occurring in non-gangrenous appendicitis which was corrected when the appendix was removed and even before the patient had recovered from the anesthesia. Other cases in his experience of appendicitis and bradycardia are cited in which gangrene did not occur but abscess and adhesions were present. He emphasized the importance of observing the pulse and temperature relation in making a prognosis and determining the time for operation.

Vaquez⁴ suggested the use of atropine to differentiate reflex bradycardia from that associated with a myocardial lesion of infectious origin. He reported a case in which a nervous patient in the course of an attack of appendicitis had considerable and persistent slowing of the pulse (40 per minute) with slight syncopal attacks. Atropine doubled the pulse rate and both the bradycardia and the syncope disappeared. Apparently, on the basis of this experience Vaquez and Lairdlow⁵ state that "it has been asserted that the bradycardia is a sign of danger, but this is an error. In one of our patients the bradycardia disappeared after the injection of atropine." These authors point out that bradycardia occurs in many different diseases, notably abdominal diseases and especially in appendicitis.

Loeper⁶ reported a fatal case of appendicitis with bradycardia, that of a man, aged 38, with sudden onset of vomiting following right lower quadrant pain and fever. Improvement followed upon the application of an ice cap.

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From the Medical Service of Dr. Mitchell Bernstein and the Surgical Service of Dr. Ralph Goldsmith, Jewish Hospital.

On the third day, abdominal distention occurred, with pinched facies. The pulse which was 110 per minute lowered suddenly to 50 per minute despite the persistence of fever. Laparotomy revealed a gangrenous appendix and a collection of pus. Although drainage was instituted, a subphrenic abscess and right pleurisy followed and death occurred on the eleventh day after operation.

Benard⁷ studied the bradycardia in appendicitis by phlebogram tracings.

Decourt and Bascourret⁸ observed that the concept of bradycardia of gastrointestinal origin seems much less well established than the usually accepted belief that certain gastrointestinal conditions may reflexly produce palpitation, precordial pain, tachycardia and extrasystoles.

THE MECHANISM OF THE REFLEX BRADYCARDIA

The mechanism of reflex bradycardia is explained by Howell⁹ as follows: "The inhibitory fibers of the heart may be stimulated reflexly by action upon various sensory nerves or surfaces. One of the first experimental proofs of this fact was furnished by Goltz's¹⁰ often quoted 'Klopfversuch'. In this experiment, made upon frogs, the observer obtained standstill of the heart by light, rapid taps on the abdomen and the effect upon the heart failed to appear when the vagi were cut. In the mammals every laboratory worker has had numerous opportunities to observe that stimulation of the central stumps of sensory nerves may cause a reflex slowing of the heart beat. The effect is usually very marked when the central stump of one vagus is stimulated, the other vagus being intact. The vagus carries afferent fibers from the thoracic and abdominal viscera, and most observers state that the heart may be reflexly inhibited most readily by stimulation of the surfaces of the abdominal viscera, by a blow upon the viscera, for example, or by sudden distention of the stomach. In man similar results are noticed very frequently. Acute dyspepsia, inflammation of the peritoneum, painful stimulation of sensory surfaces, the testes, for instance, or the middle ear, may cause a marked slowing of the heart,—a condition designated as bradycardia. What takes place in all such cases is that the efferent impulses carried into the central nervous system reflexly stimulate the nerve cells in the medulla which give origin to the inhibitory fibers of the heart."

The perennial question of the differential diagnosis between thoracic disease with abdominal symptoms and vice versa still remains an important problem in medicine. For instance, a case in point is acute coronary occlusion with its referred abdominal symptoms which often simulate gall-bladder disease. In our patient, the first symptoms suggested an acute surgical abdominal condition, but with the temporary subsidence of the abdominal symptoms, and the persistence of the bradycardia, it appeared that we were dealing with some cardiac derangement. However, the true nature of the process soon became apparent with the localization of the pain and the tenderness.

CASE REPORT

F. M., an unmarried man, aged 30, was admitted to the accident ward of the Jewish Hospital on December 22, 1935 at 4 a.m., complaining of severe abdominal pain which had come on rather suddenly and had persisted for over two hours. The pain which was quite diffuse was of a dull aching character. Flatulence and belching were present but there was no nausea or vomiting. On admission, the patient's

temperature was 95° F, and the respirations were 16 per minute. A striking feature on examination was the cardiac rate which was recorded at 44 per minute. The cardiac examination otherwise was negative. The systolic blood pressure was 120 mm of Hg and the diastolic pressure was 80 mm. Physical examination other than the foregoing was essentially negative.

The patient stated that he had had "encephalitis" for two weeks in 1922, from which he had apparently recovered. His tonsils had been removed in that year. He could not recollect any history of chorea, rheumatic fever or cardiac disease.

Following the routine physical examination, a fluoroscopic examination of the abdomen was made and was reported as negative.

At 11:30 a.m. seven and a half hours following admission to the accident ward the patient appeared quite comfortable and was free of pain. Curiously enough the bradycardia persisted, the heart rate averaged 42 beats per minute. Electrocardiographic study (figure 1) made at that time showed a sinus bradycardia of normal rhythm and a cardiac rate varying from 42 to 53 per minute.

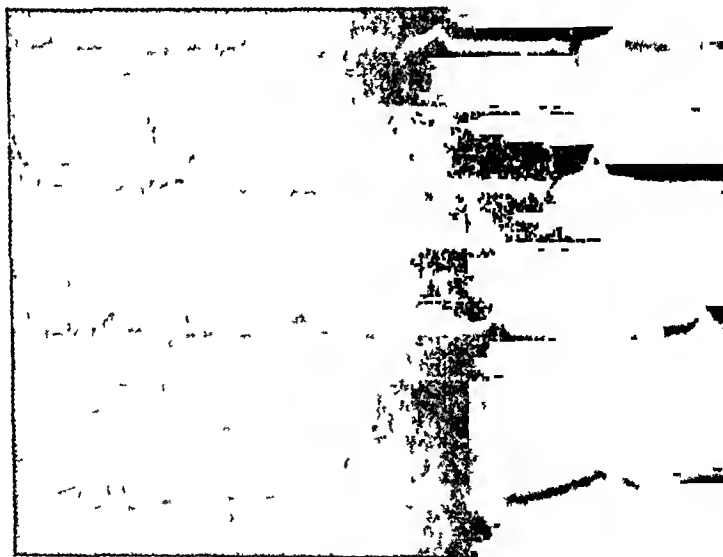


FIG 1 Sinus bradycardia with ventricular rate varying from 42 to 53 per minute

In view of the bradycardia associated with the acute abdominal symptoms, the patient was advised to remain in the hospital and he was admitted to the medical service of Dr. Mitchell Bernstein.

A blood count showed 10,850 leukocytes and 61 per cent polymorphonuclear cells, 36 per cent lymphocytes, two transitional cells and one eosinophile. Examination of the urine was normal.

On the afternoon of December 23, the day following admission, the patient again complained of pain, now localized to the right lower abdominal quadrant. Examination disclosed tenderness and muscular rigidity over this region, and the diagnosis of appendicitis was made. At 3 p.m. the cardiac rate rose to 70 per minute while the temperature was 102.6° F. A second electrocardiographic study (figure 2) showed a normal sinus rhythm with a cardiac rate of 68 per minute. The blood study showed 90 per cent hemoglobin, 4,650,000 red blood cells and 13,000 leukocytes per cu. mm. with 85 per cent polymorphonuclear cells and 15 per cent lymphocytes.

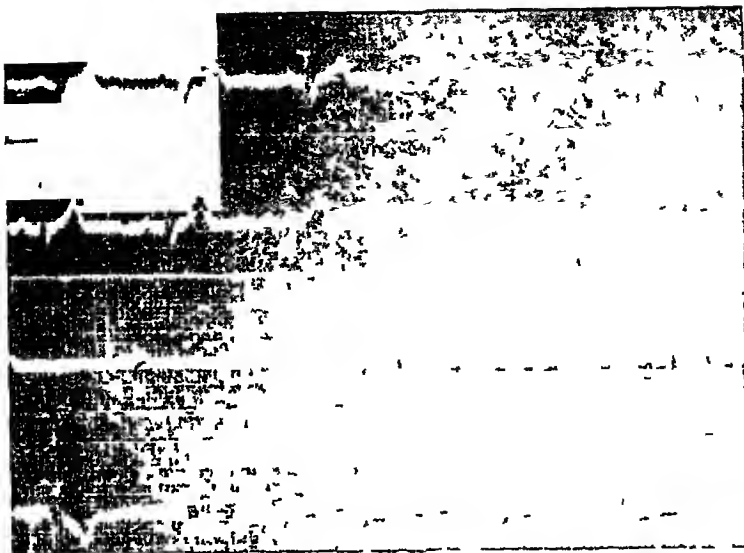


FIG 2 Normal sinus rhythm with ventricular rate of 68 per minute

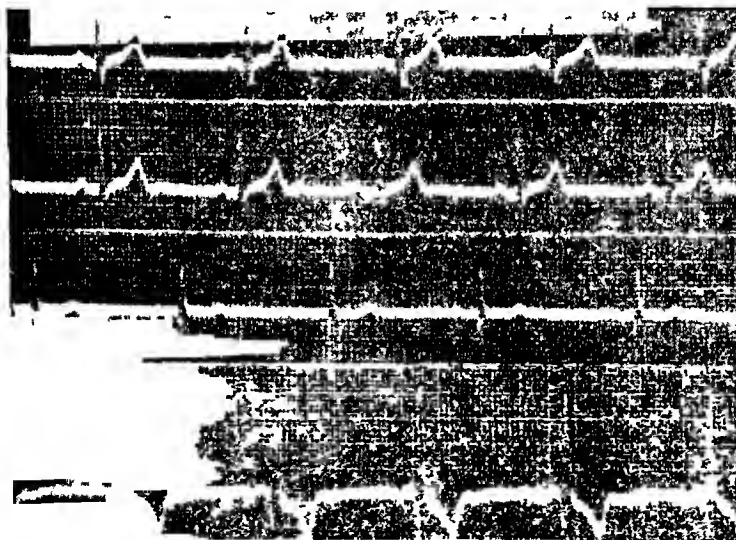


FIG 3 December 24, 1935 Following operation Sinus bradycardia with ventricular rate of 56 per minute

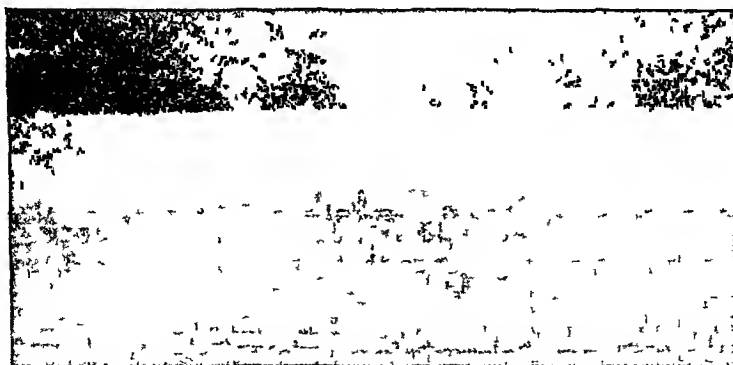


FIG 4 December 30, 1935 Seven days after operation Normal tracing with ventricular rate 77 per minute

In the early evening the patient's abdominal symptoms became more severe. Dr Ralph Goldsmith, concurring in the diagnosis of appendicitis, operated upon the patient immediately, under ether anesthesia, and removed an acute gangrenous appendix which was embedded in an omental pocket.

On December 24, the day following operation, electrocardiographic study (figure 3) curiously enough showed a cardiac rate of 56 per minute with a normal sinus rhythm. The patient's convalescence was uneventful.

Another electrocardiographic study (figure 4) on December 30, 1935, seven days after operation, showed a normal tracing with a cardiac rate of 77 per minute. Subsequent follow-up examinations of the patient on March 8, 1936 and July 2, 1936 showed the patient to be well. His heart rate was 72 per minute and following slight exertion it rose to 100 to 110 per minute.

DISCUSSION

As has been stated, Kahn in his original article on bradycardia and appendicitis, believed the bradycardia to be due to the absorption of ptomaines which acted on the cardiac centers or ganglia. However, Howell's explanation of bradycardia in abdominal diseases as being due to reflex vagal stimulation, is the generally accepted viewpoint. While an understanding of this reflex mechanism is of importance, yet from a practical standpoint the interest in Kahn's paper centers in the clinical recognition of the associated bradycardia in appendicitis, in so far as it may mean the ultimate saving of human life.

That the diagnosis of gangrenous appendicitis is often difficult, especially in cases where the symptoms are latent or deceptive, is a fact well known to the experienced physician. Since the treatment of appendicitis is purely surgical, and since the treacherousness of the disease increases as the lesion progresses, any new sign or symptom useful in establishing a correct diagnosis should be carefully considered.

In our case, herein reported, the gangrenous appendicitis might have been overlooked with a probably serious result. In fact, Loeper's case of somewhat similar nature proved fatal. Although other writers such as Broca and Benard have reported occasional instances of bradycardia in cases of nongangrenous appendicitis, this does not detract from Kahn's observation.

Because of the experience with our reported case, we should like to direct attention to and reemphasize the importance of Kahn's observation, namely that bradycardia occurring in association with abdominal symptoms indicative of appendicitis, is very suggestive of gangrenous appendicitis.

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PERIARTERITIS AND ARTERITIS OF THE TEMPORAL VESSELS, A CASE REPORT *

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ARTERITIS of the temporal vessels has recently been described as a new clinical entity by Hinton, Magath and Brown¹ A case presenting similar clinical and pathologic data is the basis for this report

CASE REPORT

A married woman, white, aged 60, a housewife living in the country, entered the hospital March 1, 1935, because of pain in her temples, fever, sweats and general malaise About five weeks before admission she had noticed a tender area in front of her right ear A week later the left side of her face became swollen and tender to pressure At this time she became aware that the temporal arteries were very prominent and red and very tender Mastication was painful General malaise and weakness were pronounced, and fever and sweats were present every night She had had no recent acute infection or injury although she had been to a beauty parlor for a permanent wave a few weeks before the onset of her illness Her past history was of no importance She had been exceptionally free of respiratory and gastrointestinal disorders She had never had rheumatism, typhoid fever or malaria There were no genitourinary symptoms The menopause had occurred 12 years before There had been a moderate weight loss of six pounds during this illness Her father died from cerebral hemorrhage at sixty She gave no history of previous vascular disease

Physical examination revealed the left temporal artery to be very prominent from a point just above the temporomandibular joint for a distance of about two and a half inches It was thickened, tortuous, the caliber irregular and the surrounding tissue very hyperemic Pulsation was present throughout the course of the vessel at the time of the first examination although this became very much diminished a little later There were no palpable nodules present The right temporal artery was less acutely involved than the left but pulsation was definitely diminished The pre-auricular and postauricular glands were moderately enlarged and tender The right facial artery was somewhat indurated where it crossed the mandible but no other peripheral vessels were involved The pupils reacted normally to light and in accommodation Both nerve heads appeared normal and the retinal vessels showed about the usual change for her age Two teeth were found to have definite periapical infection The lungs were normal to physical examination The heart was not

* Received for publication August 17, 1936

grossly enlarged, a moderate tachycardia was present and a slight accentuation of the aortic second sound. A definite pulsation was felt in the suprasternal notch. The blood pressure was 148 systolic and 90 diastolic. A careful search of the skin and mucous membranes revealed no petechiae. The reflexes were intact and normal throughout and the vibration sense normal. The spleen and liver were not palpable and there were no masses, no fluid and no tender areas in the abdomen. Digital examination of the pelvis and rectum was negative. The average of several blood counts was as follows: Hemoglobin 71 per cent, red blood cells 3,580,000, white



FIG 1

blood cells 8,600, with a normal differential. The coagulation and bleeding times and the platelet counts were normal. The Wassermann test was negative. Two blood cultures were negative. Agglutination tests for undulant fever, typhoid and paratyphoid were all negative. Several urine specimens at the time of admittance contained a faint trace of albumin and an occasional hyaline and granular cast, later specimens were negative. The phthalein test was 59 per cent in two hours and the urea clearance was 52 cc. The basal metabolic rates were minus five and three. Roentgen-ray of the chest revealed a normal sized heart and a mild fibrosis throughout both lung fields. The temperature ranged from normal to 101.8° F with

a very irregular curve. The pulse rate varied from 90 to 120. At no time were there any abdominal symptoms, peripheral nerve pains or involvement of the joints. The patient was kept at rest in bed and hot moist compresses of magnesium sulphate solution were applied to the temporal arteries. Sodium salicylate and Lextron were given orally. On March 29, a section of the right temporal artery three centimeters in length was removed. Cultures were made of the tissue on various types of media and sections made for histological study. The microscopic examination made by Dr. H. M. Banks was reported as follows: "Sections taken through four levels of the cross section of the temporal artery show a structure which is almost devoid of lumen. The intima is markedly hypertrophied, narrowing the lumen to a very small

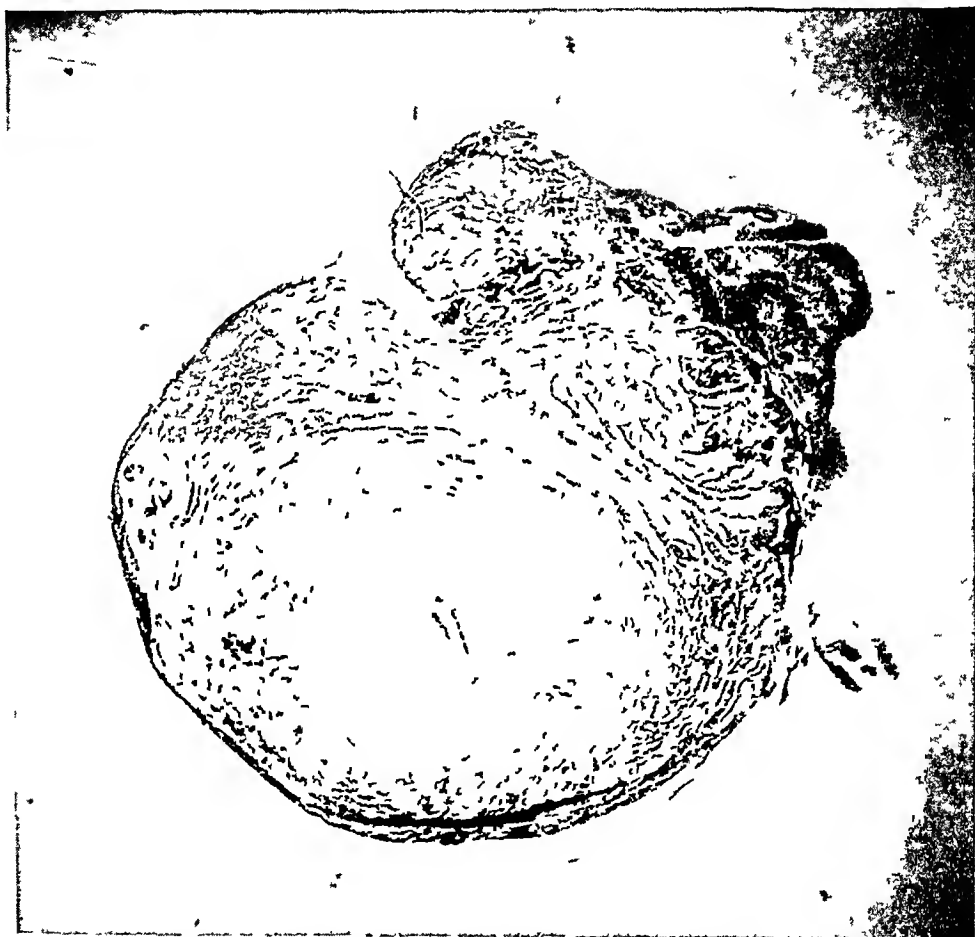


FIG 2 Low power showing temporal artery characterized by (1) narrowing of lumen, (2) massive hypertrophy of vessel wall, (3) edema of connective tissue surrounding the arterial wall and inflammatory cell infiltration of this connective tissue

point. The structure is homogeneous, somewhat hyalinized, and there is rather a scarcity of nuclear elements in the intima. The media shows almost total destruction and replacement by inflammatory cells of fibroblastic variety and by cicatrix formation. Immediately upon the exterior border of the media one finds in certain zones huge cells, irregularly round in contour, possessing many nuclei. These have the appearance of multinuclear native giant cells. The adventitia is quite narrow and atrophic in general appearance. The vasa vasorum shows hypertrophy of the muscular walls with some round cell infiltration. Cultures made from the specimen removed yielded a growth of *Staphylococcus aureus*."

It would seem significant that following the removal of this segment of diseased artery the temperature became normal and remained so until the patient left the hospital a week later. About one week after leaving the hospital there was a recurrence of fever but no local symptoms. The patient returned to the hospital on May 13 for examination. She had gained considerably in strength and her general appearance was much improved. She had had no fever after the first week. The incision over the right temporal artery was healed. The left temporal artery was smaller although it still showed evidence of inflammation. Pulsation was absent. There were no subcutaneous nodules, the eyegrounds were normal and the spleen not palpable. The remaining physical findings were the same as on the first admittance. The blood count had not changed and several specimens of urine were normal. The electrocardio-



FIG 3 Showing multinucleated giant cell formation in adventitial tissue inflammatory reaction

gram was essentially normal. The blood pressure was 166 systolic and 86 diastolic. There was considerable pulsation in the suprasternal notch. A rather extensive pocket was found about one tooth and culture yielded *Streptococcus viridans*. The temperature ranged from normal to 99.6° and the pulse rate from 90 to 130. After dental extractions the patient left the hospital on May 17, 1935. She was seen again August 6, 1935, at which time she stated she felt very well in every way. The blood pressure was 160 systolic and 110 diastolic. The left temporal vessel appeared normal and there was a normal pulsation present. At this time there appeared to be increasing narrowing of the retinal vessels and more pulsation in the suprasternal notch. Our impression at this time was that she presented evidence of a mildly progressive vascular sclerosis. Examination in June 1936 revealed essentially the same findings as the year before. No local recurrence was noted.

In making a final diagnosis in this case one must consider periarteritis nodosa and a localized periarteritis as described by Brown. The clinical course and the histologic picture do not appear to closely simulate periarteritis nodosa. The description of this generalized arterial disease as given in the writings of Kussmaul,² Gruber,³ Rothstein,⁴ Wiener,⁵ Lindberg,⁶ Singer,⁷ Friedberg and Gross,⁸ Curtis and Coffey,⁹ Hausei,¹⁰ Barnard and Burbury,¹¹ Manges and Baehr,¹² and others is that of a widespread involvement of the smaller vessels of the kidneys, heart, lungs, pancreas, mesentery, nerves, muscles and subcutaneous tissues. Since our patient presented no symptoms which might lead one to think of a generalized involvement we were more interested in those cases of arterial disease which presented subcutaneous lesions. Herlitz¹³ reported superficial

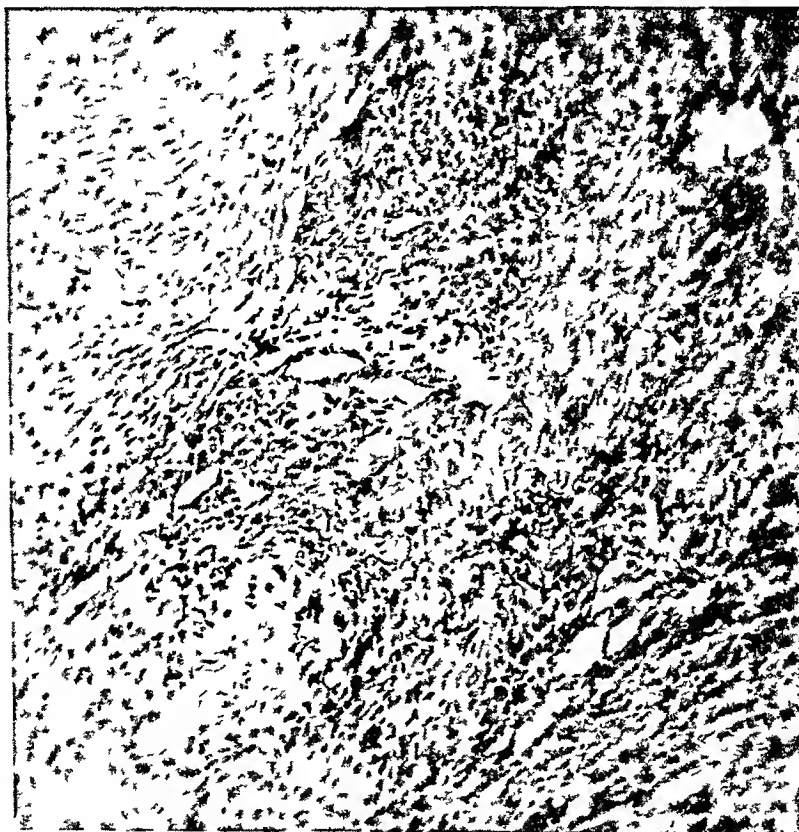


FIG 4 Showing the small round cell diffuse infiltration of media and adventitia, also fibroblastic cell reaction

nodules in 12.5 per cent of his cases of periarteritis nodosa. Lindberg⁶ presented in detail a case of a young girl who apparently recovered after several exacerbations of joint pains, fever, anemia and numerous subcutaneous nodules which on section proved to be typical examples of periarteritis nodosa. He also reviewed 20 cases from the literature all being very similar in clinical and pathological detail. We could find no resemblance to our case in any of these

CONCLUSION

A case is presented of localized arterial disease involving the temporal arteries which appears to be separate and distinct from the generalized condition of periarteritis nodosa.

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EDITORIALS

THE MEETING AT ST LOUIS

THE Twenty-first Annual Session of the American College of Physicians at St. Louis was in every way a very successful meeting. The total registration, 2,321, places it as the second in size of attendance among all gatherings of the College up to this time. This figure has been surpassed only at the Philadelphia meeting in 1933 where 2,444 were registered. Moreover it was noteworthy that a very large proportion of those in attendance remained until the closing day.

Of the Regents of the College 21 out of 23 were present, and 49 of the 57 Governors either attended or sent representatives.

Throughout the meeting the large hall which housed the General Sessions was almost completely filled each afternoon. The Morning Lectures also drew a large attendance. The Round Table Discussions at the noon hour were an innovation in the program this year. They proved a most popular feature, more than four times the available number of tickets were applied for.

The clinical program provided by the hospitals and medical schools was of an unusually even grade of excellence. Seldom has more enthusiasm been expressed by the members than was brought out in discussions of these carefully arranged clinical meetings. They remain in the minds of the majority the most valuable single feature of our annual session.

St. Louis through its medical representatives greeted the College with warm and gracious hospitality and spared no pains in careful preparation for our reception. All who attended will look back with pleasure upon the days spent in the care of such thoughtful hosts and will hope that they will feel repaid by the gratitude of our members and the manifest success of their undertaking.

THE ANNIVERSARY VOLUME IN HONOR OF DR JOSEPH HERSEY PRATT

IN this number of the *ANNALS OF INTERNAL MEDICINE* there appears a group of articles surmounted by a heading which indicates that they are contributed as the writers' part of an Anniversary Volume in honor of Dr. Joseph Hersey Pratt.

Dr. Joseph Hersey Pratt of Boston, who is widely known among the medical men of this country, will reach his sixty-fifth birthday this year. It was the desire of a large number of his friends to honor this occasion by the presentation to him of an Anniversary Volume. It was his own wish that the valuable contributions to be made to this volume should not be

barred from publication elsewhere as well, in a journal which would ensure their accessibility to the general medical public

By agreement with the Committee in charge of the Anniversary Volume the Annals will publish in the coming months such articles contributed as are judged by the Editor to fall within the field of this journal. This plan, it is felt, will bring before our readers many interesting papers and will at the same time increase the permanent value of these contributions. It is an added pleasure to the Board of Editors that through this arrangement the ANNALS is of service to those who are responsible for this signal honor to an eminent physician

REVIEWS

Urological Roentgenology By MILEY B WESSON, M D, and HOWARD E RUGGLES, M D 269 pages, 24 × 15.5 cm Lea and Febiger, Philadelphia, Pa 1936 Price, \$5.00

Urological Roentgenology is a small volume "prepared to meet the needs of the physician who wants to learn to interpret urograms" It is a 269 page book with 227 engravings There are interesting chapters dealing with the history of urography and its detailed technic in the beginning, while the rest of the book is devoted to the diagnosis and interpretation of urograms covering the entire urogenital tract The illustrations are excellent and not only useful, but essential in arriving at diagnoses of conditions in this tract

Intravenous pyelography is discussed and depicted, its value and limitations are brought out carefully in contra-distinction to retrograde pyelography Some very unusual pyelo-ureterograms of anomalies are shown indicating how easy it is for abnormal organs to undergo pathological changes Also how essential it is to know the exact status of the upper urinary tract before surgery is undertaken, for example, it is necessary to know that there are *two* kidneys before removing *one*

The usual pathological conditions of the kidney are well shown by pyelograms with descriptive footnotes Many of the rare conditions, such as echinococcal cysts and actinomycosis of the kidney are also included

The chapter on traumatism of the urinary tract suggests helpful methods by which the extent of the injury as well as the part of the urinary tract involved may be determined Neurological lesions involving the urinary tract are also discussed

While this book is of unquestioned merit, still it must be borne in mind that no two pathological conditions of the urinary tract are the same and for this reason no two urograms are the same, so diagnoses of urograms may be extremely difficult of interpretation In other words, urograms must be regarded only as additional diagnostic information and not the sole dependency If the physician regards this volume in this light it should be helpful

W H T

A Hand-Book of Ocular Therapeutics By SANFORD R GIFFORD, M D Second Edition 341 pages, 20.5 × 14 cm Lea and Febiger, Philadelphia, Pa 1937 Price, \$3.75

It is with pleasure that we welcome a second edition of this monograph on Ocular Therapeutics The work has been enlarged from 272 pages to 341 pages Additions have been made in the field of vitamin and food therapy and also in that of the use of the various internal secretion extracts in the field of ophthalmology

The application of the different means of physical therapy and the evolution of their use has also been brought up to date The correction of an error in the table for tuberculin dilutions will be welcomed by those using the book as a guide in this type of work The reviewer feels that an initial dose of 1/50,000 mgs of tuberculin as recommended for treatment of a retinal lesion is far too great and may cause very definite damage in a few very sensitive patients

The author and publishers are to be commended for this excellent work which can be recommended as a guide both for the ophthalmologist and the general man who may be called upon to render service in many eye conditions

C A C

The Clinical Use of Digitalis By DRLW LUTEN, M D, Associate Professor of Clinical Medicine, Washington University School of Medicine Indexed 226 pages, 23.5 × 15.5 cm Charles C Thomas, Springfield, Ill and Baltimore, Md 1936 Price, \$3.50

The more recent explanations of the pharmacological and clinical action of digitalis are presented in this volume. The author emphasizes that the clinical indication for the use of this drug is primarily congestive heart failure, no matter what the heart rhythm may be. He also points out that its continued use tends to prevent subsequent failure in a heart which has failed at one time. It would seem to be of use in preventing failure, when such a state might be assumed to be imminent. The reviewer highly recommends this book to practitioners, especially that part which deals with the clinical use of digitalis. As regards some of the considerations of the mode of action of digitalis, at times the argument seems more specious than convincing.

W S L, JR

A Text-Book of Neuro-Anatomy By ALBERT KUNTZ, M D Second Edition 519 pages, 24 × 16 cm Lea and Febiger, Philadelphia, Pa 1936 Price, \$6.00

This book is a straight-forward presentation of facts in text book form. It avoids discussion of debatable subjects, and bibliographic references are to all intents and purposes completely absent in the text though a short list of collateral subject matter is found at the end of each chapter. With this set up the author has been able to cover an astonishing breadth of field in a medium sized text. Thus phylogeny and embryology are featured as an introduction and the embryology of the brain is further discussed in the section dealing with the brain.

The usual sequence of presentation is followed, consideration of neural histology and morphology preceding the detailed internal structure of the central nervous system. The latter is attacked in the order of spinal cord, brain stem and cerebellum and finally the forebrain. Each subtitle, a e, the cranial nerves, ends with a short, but not too short, summary of the subject.

The subject matter is brought up to date, particularly that featuring Cannon's fundamental contributions to the physiology of the autonomic system. The analysis of the cerebral cortex is clear, concise and convincingly illustrated—an altogether useful presentation. A similar success in dealing with the basal nuclei is conspicuously lacking, one leaves this subject with a scant grasp of the significance of these centers.

The clear and abundant illustrations are enriched by numerous Nissl preparations of nuclear areas, a visual asset all too often neglected in this type of work.

Clinical application of neuro-anatomy is presented through description of a series of representative lesions of the nervous system with an analysis of their significance. The book ends with a concise laboratory manual of the dogfish and human brain. One may term this a useful and practical presentation of a difficult subject.

C L D

The Practitioner's Library of Medicine and Surgery Supervising Editor, GEORGE BLUMER, M A (Yale), M D, F A C P, David P Smith Clinical Professor of Medicine, Yale University School of Medicine, Consulting Physician to the New Haven Hospital *Volume XI Eye, Ear, Nose and Throat* Associate Editors ARTHUR M YUDKIN, M D, Clinical Professor of Ophthalmology, Yale University School of Medicine, and PAUL B MACCREADY, M D, F A C S, Assistant Clinical Professor of Otolaryngology, Yale University School of Medicine Lxvii + 1153 pages, 402 illustrations 25 × 17 cm D Appleton-Century Company, New York 1937 Price, \$10.00 a volume

The eleventh volume of *The Practitioner's Library*, like its predecessors which have been reviewed from time to time in the ANNALS, relates the essential material of certain special phases of Medicine to the experiences of the clinician in his daily practice. Thus it presents those diseases of the *Eye, Ear, Nose and Throat* which the general practitioner may encounter at any time, which he can diagnose, and which, for the most part, can be treated adequately by standard, proved methods and with the means readily available to the physician who has a large and varied group of patients. Diagnosis and treatment are emphasized. When major operative procedures are discussed it is with the thought of giving the practitioner such background material as will make it proper for him to advise his patients as to what may properly be expected from those who are recognized specialists in the field in question. This volume, therefore, presents that material which is more or less constantly needed by every practitioner, and which he must have available if he is to serve his clientele adequately in respect to the affections of the special sense organs and related structures.

To this volume there have been 43 contributors, chosen largely from the younger workers in these special fields. The subject matter is divided into four main parts, with about 385 pages devoted to diseases of the Eye, 275 to the Ear, 250 to the Nose, 125 to the Pharynx and 90 to the Larynx. Numerous, and usually well-chosen, illustrations are utilized throughout. Considering the avowed purpose of the book, it must be questioned whether the space occupied by the many low-power photomicrographs in chapter XVII, dealing with the histopathology of the ear, could not have been used to better advantage otherwise. Although obviously prepared from beautiful specimens, such figures require considerable expert knowledge for their appreciation.

As the reviewer has had occasion to mention in respect to earlier volumes of this series, typographical slips are very few for a first edition. A misspelled word in a running head throughout chapter XLV, will offend the eye of a critic, no matter how kindly disposed he may be. The general press work is excellent, the binding substantial and attractive and the index adequate. It is impossible to evaluate the individual chapters provided by the many contributors, but the work as a whole is a worthy member of this series, and will prove a valuable aid to every practitioner of Medicine.

C V W

Being Born. By MRS FRANCES BRUCE STRAIN, Associate Educational Director, Cincinnati Social Hygiene Society. Cloth Price, \$1.50. Pp 144, with 28 illustrations. New York & London: D Appleton-Century Co., 1937.

This book is written by a mother for her children, and covers all the essentials on the subject of human reproduction. It is written especially for the pre-adolescent boy and girl, and is presented in a very sane and healthy manner. There are twelve chapters and "a list of words and their meanings." Most of the material is in the form of questions and answers, which is the best way of presenting the subject to children.

This book can be highly commended for avoiding the abnormal, which unfortunately is introduced in most books on sex, even for children. A few parents might hesitate to tell their children about coitus, or as Mrs. Strain says "mating is not only a way to start one's family, but is also a way of expressing their love, husbands and wives unite when no baby is to be started," but her discussion of this subject cannot cause offense.

The author has covered almost every question that a normal, questioning and curious youngster might ask. She does not beat about the bush, tells how, why, and where babies come into being. The physician certainly can recommend this book to all parents.

J L McC

COLLEGE NEWS NOTES

NOMINATING COMMITTEE FOR 1937-38

In accordance with Article I, Section 3, of the By-Laws of the American College of Physicians, the President, Dr J H Means, has appointed the following Nominating Committee for 1937-38

Dr Jonathan C Meakins, Montreal, Que , *Chau man*,
Dr James B Herrick, Chicago, Ill ,
Dr Alexander M Burgess, Providence, R I ,
Dr A Comingo Griffith, Kansas City, Mo ,
Dr William R Houston, Austin, Tex

The first two names are appointments from the Board of Regents, the second two names are appointments from the Board of Governors, the last name is an appointment from the Fellowship at large

NEW LIFE MEMBER

Dr Estella G Norman (Fellow), Miami Springs, Florida, became a Life Fellow of the American College of Physicians on April 27, 1937

Books

Dr James H Means (Fellow), Boston, Mass , "The Thyroid and its Diseases",
Dr Ralph Pemberton (Fellow), Philadelphia, Pa , "Arthritis and Rheumatoid Conditions",
Dr William R Houston (Fellow), Austin, Tex , "The Art of Treatment",
Dr William Gerry Morgan (Fellow), Washington, D C , "Functional Disorders of the Gastro-intestinal Tract"

REPRINTS

Dr H Sheridan Baketel (Fellow), Jersey City, N J —1 reprint,
Dr Grafton Tyler Brown (Fellow), Washington, D C —1 reprint,
Dr C T Burnett (Fellow), Denver, Colo —15 reprints,
Dr A Morris Gmsberg (Fellow), Kansas City, Mo —1 reprint,
Dr Jacob Gutman (Fellow), Brooklyn, N Y —1 copy, tenth supplement to "Modern Drug Encyclopedia",
Dr Arthur M Master (Fellow), New York, N Y —2 reprints,
Dr Sydney R Miller (Fellow), Baltimore, Md —1 reprint,
Dr Kenneth Phillips (Fellow), Miami, Fla —1 reprint,
Dr William R Rawls (Fellow), New York, N Y —1 reprint,
Dr Paul H Ringer (Fellow), Asheville, N C —1 reprint,
Dr Felix J Underwood (Fellow), Jackson, Miss —1 reprint,
Dr L B Carruthers (Associate), Miraj, India —1 reprint ,
Dr George B Dorff (Associate), Brooklyn, N Y —8 reprints,
Dr Stuart L Vaughan (Associate), Buffalo, N Y —1 reprint,
Dr Walter A Bastedo (Fellow), New York, N Y —3 reprints,
Dr A B Brower (Fellow), Dayton, Ohio —1 reprint,
Dr A Allen Goldbloom (Fellow), New York, N Y —2 reprints,
Dr Charles H Lutterloh (Fellow), Hot Springs, Ark —2 reprints,
Dr Philip B Matz (Fellow), Washington, D C —1 reprint,
Dr Oliver T Osborne (Fellow), New Haven, Conn —1 reprint,

Dr Joseph F Painton (Fellow), Buffalo, N Y—5 reprints,
 Dr Paul A Draper (Associate), Colorado Springs, Colo—2 reprints

MEETING OF SOUTHERN CALIFORNIA MEMBERS

Seventy-five of the Southern California members of the College held a dinner meeting at the California Club, Los Angeles, on March twentieth, 1937 Dr Egerton L Crispin, former Governor and present Regent of the College, presided Dr F M Pottenger, ex-president, spoke upon the certification of internists and other matters pertinent to the College, Dr Wm J Kerr, San Francisco, now president-elect of the College, delivered an interesting address upon the future of the College in the advancement of medicine

TESTIMONIAL DINNER TO DR RIESMAN

Dr David Riesman (Fellow) was guest of honor at a dinner on the evening of March 25, 1937, at the Bellevue-Stratford Hotel, Philadelphia, attended by more than two hundred and fifty of his professional friends on the occasion of his seventieth birthday Guest speakers included Provost Josiah Penniman of the University of Pennsylvania, Dr Alfred Stengel (Master), Dr Henry A Christian (Fellow) of Boston, Dr Lewis A Conner (Fellow) of New York City, Dr Wilmer Krusen of the Philadelphia College of Pharmacy and Science, Dr Wm Gerry Morgan (Fellow) of Washington, and Dr Walter C Alvarez (Fellow) of Rochester, Minn Dr Russell Boles (Fellow) of Philadelphia was toastmaster Dr Stanley C Harris announced that friends of Dr Riesman had made possible the publication of a volume of his selected writings to celebrate his birthday An engraved plate, bearing the names of Dr Riesman's former and present assistants, was presented by Dr Thomas Fitz-Hugh, Jr (Fellow) Dr Riesman responded with a characteristically delightful account of his medical career and of his view of the present and future of medicine envisioned from the vantage point of his "seventy-year-high mountain top"

Dr Albert E Russell (Fellow), U S Public Health Service, Washington, D C, gave the Second Annual Harold S Boquist Memorial Lecture at the University of Minnesota Medical School, Minneapolis, on December 6, 1936

The Annual Meeting of the California Tuberculosis Association was held at Riverside, California, April 1-3, 1937 Dr R H Sundberg (Fellow), San Diego, was chairman of the program committee, Dr F M Pottenger (Fellow), Monrovia, was vice president, Dr Chesley Bush (Fellow), Livermore, Dr R L Cunningham (Fellow), Los Angeles, and Dr W C Voorsanger (Fellow), San Francisco, were directors of the Association Dr Sidney J Shipman (Fellow), San Francisco, acted as chairman of one of the clinical sections, and discussed the paper on bronchial stenosis Dr Robert A Peers (Fellow), Colfax, presented a paper on "Routine Tuberculin Testing in Schools The Part Played by the Medical Profession", Dr Lvell C Kinney (Fellow), San Diego, presented a paper on "Diagnosis of Tuberculosis of the Intestinal Tract", Dr Munford Smith (Fellow), Los Angeles, presented a paper on "Relationship of Trauma to Tuberculosis," said paper being discussed by Dr Philip H Pierson (Fellow), San Francisco, and Dr R L Cunningham (Fellow), Los Angeles, Dr Carl R Howson (Fellow), Los Angeles, presented a paper on "Differential Diagnosis of Diseases of the Chest," said paper being discussed by Dr Munford Smith (Fellow), Los Angeles, and Dr Harold G Trimble

(Fellow), Oakland, Dr Harold G Trimble (Fellow), Oakland, with Dr B H Wardrip, presented a paper on "Pneumoperitoneum—Its Use in Pulmonary Tuberculosis," said paper being discussed by Dr E W Hayes (Fellow), Monrovia, Dr Philip H Pierson (Fellow), San Francisco, discussed the paper on "Simultaneous Bilateral Pneumothorax in the Treatment of Pulmonary Tuberculosis"

The Tenth Annual Graduate Fortnight of the New York Academy of Medicine will be held November 1-12, 1937, and will be devoted to a consideration of medical and surgical disorders of the urinary tract. The subject will include Bright's disease, arterial hypertension, and infections, tumors, calculi and obstructions of the urinary tract, and will exclude venereal disease and gynecology. For the Annual Fortnight a subject of outstanding importance in the practice of medicine and surgery is selected and is presented from as many angles as possible.

The program is under the general direction of the Committee on Medical Education. The following Fellows of the College are members of this Committee: Dr Walter P Anderton, Dr F Warner Bishop, Dr Ralph H Boots, Dr Arthur F Chace, Dr Emanuel Libman, Dr Thomas T Mackie, Dr Herman O Mosenthal, Dr Bernard S Oppenheimer, Dr Maximilian A Ramirez, Dr Willard C Rappleye, Dr Howard F Shattuck, Dr Charles F Tenney and Dr John Wyckoff.

Dr Ralph Pemberton (Fellow), Philadelphia, delivered a series of lectures on "The Modern Outlook upon Arthritis," including the Hartford (Conn.) Medical Society on April 5, the Lycoming County (Pa.) Medical Society at Williamsport, Pa., on April 9, and the New Castle County (Del.) Medical Society at Wilmington, Del., on April 20. Dr Pemberton also addressed the Health Institute sponsored by the Women's Auxiliary of the Philadelphia County Medical Society on April 13 on "Arthritis, and the Problem of Control."

Dr Anthony C Cipollaro (Associate), New York City, has been recently appointed consulting dermatologist at the St. Joseph's Hospital of Far Rockaway.

OBITUARIES

DR CHARLES VINCENT NIEMEYER

Dr Charles Vincent Niemeyer, Fellow, 4610 Hudson Boulevard, Union City, N J, died January 11, 1937, of myocarditis following a collapse in his office six weeks before, at the age of 48

Dr Niemeyer, the son of Carl H and Katherine Niemeyer, was born in New York City, March 7, 1888. He attended public and private school in New York City, and graduated from the University of Vermont, M D, 1912. He served as Intern in Red Cross and St Vincent's Hospital and five years in St Mary's Children Clinic in New York City. In 1914 he moved to Union City, N J, where he began the practice of his profession. In the same year he began the first Baby Welfare Station in North Hudson County and established seven Baby Stations in Monmouth County in 1919. He limited his practice to Pediatrics in 1917, being the first in North Hudson County to do so.

In 1929-32 he did post-graduate work in Vienna, Berlin, London, Mt Sinai of New York, Boston and Chicago.

Rejected during the World War, he organized a Red Cross Chapter for North Hudson and devoted much effort to it. He was a Charter Member of North Hudson Physician's Society, acting as President for one term and as Secretary for fifteen years. He was a member of Osler Medical Society, Hudson County Medical Society, New York Academy of Medicine, New Jersey State Medical Society, American Pediatric Society, American Medical Association, and a Fellow of the American College of Physicians since 1931.

At the time of his death, he was Chief of the Pediatric Staff, St Mary's Hospital, Hoboken, N J, Consultant to St Mary's Hospital and Attending Physician to North Hudson Hospital, Consultant to Christ's Hospital, Jersey City, and to Nyack General Hospital.

He was a member of St Augustine Church, Fourth Degree Knight of Columbus, member of the Newman Club, Kiwanis Club and the Nu Sigma Nu Medical Fraternity. In 1920 he married Caroline Salenius, who survives him.

In so short a span of life, he accomplished much. The Community and the Profession have suffered a great loss in his untimely death.

CLARENCE L. ANDREWS, M D, F A C P,
Governor for New Jersey

DR WILLIAM LAFAYETTE RICH

Dr William Lafayette Rich (Fellow), Salt Lake City, Utah, died November 17, 1936, of chronic myocarditis, aged, fifty-eight years.

Dr Rich was born June 17, 1878, at Montpelier, Idaho, and for a number of years had followed the specialty of dermatology. He attended the

Weber State Academy, Ogden, Utah, and the Bear Lake Academy, Paris, Idaho, and later, the Utah Agricultural College at Logan, Utah. He was graduated from Washington University School of Medicine, St. Louis, in 1907, and was certified by the American Board of Dermatology, June 11, 1934. He had pursued postgraduate study at the London Hospital Medical College (University of London), Middlesex Hospital, London, Charing Cross, St. Barth, St. Mary's and other London institutions. In addition, he did postgraduate work at the Vanderbilt Clinic, New York City, and at the New York Postgraduate Medical School.

For several years, Dr. Rich had been chief of the Dermatological Clinic, Salt Lake General Hospital, dermatologist, Dr. W. H. Groves Latter-Day Saints Hospital, St. Mark's Hospital, the U. S. Veterans Administration Facility, and the D and R-G and Western Pacific Railway. He was a Captain, Medical Officers Reserve Corps, and during the World War was a member of the National Advisory Board. He was a former president and a former secretary of the Utah State Medical Association, and a member of the House of Delegates of the American Medical Association in 1923. Dr. Rich had been an active and interested Fellow of the American College of Physicians since 1920.

Dr. Rich was one of the best liked physicians by his colleagues in his city. He had always been active in medical society affairs and enjoyed a large consultant practice up to the time of his death. One of his chief characteristics was that he served as a peace maker. He took an active interest in child welfare work. He will be mourned by many patients as well as by his colleagues.

L. E. VIKO, M.D., F.A.C.P.,
Governor for Utah

DR. B. H. FRAYSER

Benjamin Hobson Frayser, born, Buchanan, Va., October 7, 1887, attended public schools of Charlottesville, Va., Cleveland's Private School, Pantops Academy, Va., and the Fiske Military School, Va., three years, Baltimore Medical College (now University of Maryland), M.D., Lincoln Memorial University Medical Department (now University of Tennessee), 1909, Ph.G., University of the South, 1909, Intern, Pottsville (Pa.) Hospital and Chicago Lying-in Hospital, for a time connected with the Soldiers' Home Service Hospitals at Grand Rapids, at Dayton, Ohio, and at Hot Springs, S. D., also Associate Professor of Obstetrics and Instructor in Anatomy, Lincoln Memorial University, also Associate Professor, Pharmacology, University of the South, Resident Physician, Santo Tomas Hospital, Panama City, 1914-15, in 1915 entered U. S. Indian Medical Service and was in charge of health work in San Juan Hospital, Shiprock, N. M., and Government Hospital, Dulce, N. M., until 1920, from July, 1920, Passed Assistant Surgeon (R) in the following U. S. Public Health Service

Hospitals—New Haven, Connecticut, Boston, Mass., Helena, Mont., and Lexington, Ky., at time of death, Senior Medical Officer, in charge of medical and surgical sections, U S Veterans Administration Facility, Lexington, Ky., founder, Pi Delta Pi Secondary School Fraternity, member, Chi Zeta Chi, medical fraternity, Kappa Phi, pharmaceutical fraternity, Sigma Phi Epsilon and Theta Nu Epsilon fraternities, ex-President, the Association of Government Surgeons of the United States, member, American Medical Association, Association of Government Surgeons, Medical Veterans of the World War, National Reconstruction Alliance, Sons of the American Revolution, Veterans of Foreign Wars, Fellow of the American College of Physicians since March 10, 1923, author of several published papers, and former Business Manager of *The Indian Medical News*

The following information has been supplied by Dr Jo M Ferguson of the Veterans Administration, Lexington, Kentucky, who has been closely associated with Dr Frayser since March 16, 1931

"Dr Frayser was very painstaking in his work, always kind and courteous to the patients in his charge, as well as to all of the personnel with whom he was associated. There was not a physician in the hospital better liked or who was more trusted by every one than Dr Frayser. He was always genial and pleasant and willing at all times to do the most he could for his associates. He was never too busy to listen to complaints of patients and employees and to give of his time and the benefit of his training and experience to those in need of aid or advice. He was always loyal to his fellow workers and had the love and admiration of all those with whom he was associated, and his death on March 5, 1937, has been keenly felt by all."

C W DOWDEN, M D,
Governor for Kentucky

DR RANDOLPH L McCALLA

Dr Randolph L McCalla, an Associate of the College, Boise, Idaho, died October 10, 1936, of uremia, aged forty years. He was born and reared in Boise, the son of the late Dr L P McCalla.

Dr McCalla received his A B degree from Georgetown University, Washington, D C, in 1916, then took two years in medicine at Harvard University, and received his degree in medicine from Columbia University College of Physicians and Surgeons in 1920. He was an interne at St Agnes Hospital, Baltimore, 1920-21, and thereafter, successively, assistant in medicine, instructor in medicine, assistant professor in medicine and chief of the medical clinic at the University of California Medical School, 1924-29. He was house officer in the San Francisco Hospital during 1924-25, and resident physician in the University of California Hospital, 1925-27, assistant visiting physician in the same institution, 1925-29, resident physician, Laguna Honda Home, San Francisco, 1927-29. He then went to

Hawaii, where he was physician-in-charge, Lanai Plantation Hospital, 1930-34. He returned to Boise, Idaho, in May, 1936.

Dr. McCalla had been a member of the California Academy of Medicine, the Territorial Medical Society of Hawaii, and the American Medical Association. More recently, he had become a member of the local societies in Idaho. He was elected an Associate of the American College of Physicians during 1934.

He was the author of several published articles, dealing primarily with cardiology. He was a thoroughly capable internist of high integrity, possessed of an excellent medical mind, a credit to himself and to the organizations with which he was connected.

ANNALS OF INTERNAL MEDICINE

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ADDRESS AT THE ANNUAL CONVOCATION OF THE AMERICAN COLLEGE OF PHYSICIANS*

By the President of the College, ERNEST B BRADLEY, F A C P,
Lexington, Kentucky

It seems impossible that you should have chosen me, even for one year, to be the President of the American College of Physicians. No greater distinction could come to any man engaged in the practice of Internal Medicine. To me the honor is almost overpowering. All preceding presidents, with possibly one exception, have been teachers and professors of medicine, and even the one exception was a nationally known internist, who came from a great medical center. I could not claim such qualifications. To explain my selection I decided that your Board of Regents and the Nominating Committee felt it was time to show real democracy—to recognize one of that numerous class, who have not had medical honors heaped upon them.

Having been a member of your Board of Governors for a number of years and at that time its Chairman, I took the honor as one bestowed, not upon me personally, but as a recognition by the Board of Regents of the high regard in which your Board of Governors is held. Therefore, as a former Governor, I thank you for them.

Former Presidents, the list of whom includes many of the most eminent internists in the United States and Canada, have delivered addresses which have shown remarkable understanding of modern medical problems. They have explained the ramifications of medical trends and have given sound advice to the members of this organization. Some have gone quite deeply into the discussion of modern problems affecting doctors, "socialized medicine," "state medicine," "social security," etc. These economic questions are very important, but they are also very involved. It might be advisable at our next meeting to devote a whole afternoon or evening to such questions alone. I must confess that I feel incapable of dealing with them adequately, nor would I venture to discuss the various medical problems that are agitat-

* Presented at the St. Louis meeting of the American College of Physicians, April 19, 1937.

ing us today, so instead of a Presidential Address, I will try to review briefly the progress of the College during my term of office and to point out to you certain aspects that have impressed me as President. This year has taught me in what great esteem our College is held by other organizations, both lay and medical, and to appreciate the opportunities which this body has for the betterment of medical practice in America.

Except for the preparation of the program of the General Sessions, your President is more or less of a figure-head. It is for this reason, no doubt, that the College has done just as well during the past year as in any preceding one. In fact, its achievements may have been somewhat above the average. When I say that the President is a figure-head, I do not mean this too literally. He has a great deal to do. The major credit, however, should go to the Board of Regents and to the Board of Governors, who individually and through their committees give unsparingly of their time and energy. It is this cooperation that makes the duties of the President a pleasure rather than a task.

In summing up the activities of the College, attention is called first to probably our most important department—the business office. It is here that the Executive-Secretary, Mr. E. R. Loveland, with his clerical assistants take care promptly and efficiently of a vast amount of work. This office is perfectly organized and all records are kept in such a way as to be instantly available when needed. There are multitudinous details connected with applications for membership. Every candidate is investigated most carefully with respect to his qualifications, professional, social and ethical. Cards are sent to all of our members who live anywhere near the residence of the candidate, or, if he has recently changed his address, to all members near his former location. All this information is tabulated so well that the work of the Committee on Credentials is lightened as much as possible. In addition to routine business, collection of dues, etc., there is the preparation and publication of the Directory every two years. And every year there is an immense amount of work connected with the Annual Sessions. Obtaining and arranging the commercial exhibits and preparing the program are but a few of the duties that must be performed. It would be impossible for me to enumerate the many activities of our business office, but all are handled promptly, efficiently and with dignity.

In connection with the work of the business office I have mentioned the preparation and publication every other year of the Directory of our members. This is a most valuable book of reference. The last edition and supplement contains, geographically as well as alphabetically arranged, the names of 3600 physicians engaged in internal medicine and allied specialties. With its biographical data it is invaluable in referring patients to other physicians in distant cities. It is becoming more and more appreciated as a most important "Who's Who" in Internal Medicine.

While we are mentioning assets of which we are proud, your attention is called to the Journal which the College owns and controls. Under the

able Editorship of Dr Maurice Pincoffs, the ANNALS OF INTERNAL MEDICINE has shown a growth that is very gratifying. Each year it has increased in size and importance. The current volume for the twelve months will contain at the present rate almost two thousand pages of scientific reading matter, book reviews, editorials and College news. The scientific articles are not published in a haphazard way, but are chosen carefully by the Editorial Board and may be said to represent the best literature devoted entirely to internal medicine in America. There is also cause for satisfaction in knowing that the Annals is now a financial success and is more than self-supporting. In fact, last year it earned a very substantial sum.

These annual clinical sessions affording a renewal of old friendships and an interchange of medical ideas have come to be regarded by those engaged in the practice of Internal Medicine as the outstanding event of the year. Much of the success of this meeting is due to your General Chairman, Dr David P. Barr. Together with his associates on the various committees, he has worked long and faithfully to formulate the program which we are enjoying this week. The Clinics at the Hospitals are an inspiration to us all, and we shall not soon forget the hospitality that has been extended to us here in St. Louis. These people from Missouri do not "Have to be shown" how to make us feel at home. We hope that at some future time they will be willing to let us come back again.

Two projects of importance to the College had their culmination during the past year, both of them having been instigated during the year preceding. I refer, first to the organization of the American Board of Internal Medicine, and second, to the purchase of a permanent headquarters.

Initiated by the American College of Physicians, and with the cooperation of the Section on Medicine of the American Medical Association, the American Board of Internal Medicine completed its organization in June 1936 and is now actively functioning. The purpose of this Board is briefly, the certification of specialists in the field of internal medicine. The growth of specialism has called into action many similar Boards of Certification. There are now eleven such boards. They are, in the order of their establishment, the American Boards of, Ophthalmology, Otolaryngology, Obstetrics and Gynecology, Dermatology and Syphilology, Psychiatry and Neurology, Radiology, Orthopedic Surgery, Urology, Internal Medicine, and Pathology. The American Board of Surgery has completed its preliminary steps and is almost ready to function.

The plan of certifying specialists has been one of the developments of modern medicine that has resulted from the enormous growth of specialism itself. Since one could be listed as a specialist by merely claiming to be a specialist, there seemed to be no proper way to distinguish between the qualified and the unqualified. Of course, in many cases, such certification is wholly superfluous. Many specialists by reason of long and successful practice, by their hospital and medical school connections, or by the regard in which they are held by members of the medical profession familiar with

their work, will gain nothing by being certified in any particular specialty. Dr. George H. Meeker, Dean of the Graduate School of Medicine of the University of Pennsylvania has called this "casual" certification, whereas, the evolutionary tendencies in the whole medical field he says are an abandonment of the "casual" for the "systematic." It is this tendency to be more systematic that has caused the growth of these boards of certification. It is evident that certification of internists will result in changes in postgraduate work to provide for more systematic preparation for this specialty. In just what way this will be done is somewhat uncertain. However, it will result probably in a longer training in internal medicine during the years of hospital residence, with more hospitals of approved class offering residencies in medicine. Other changes will no doubt come about, the nature of which cannot be definitely foreseen at this time. In the long run it would seem that certification must result in better preparation before specialism is attempted.

Certain constitutional amendments were proposed at the December meeting of the Board of Regents and have been published in the ANNALS. They would have caused very drastic changes in the selection of new members. The first change was in Article IV, which states that "Fellows shall be members of the medical profession, engaged as practitioners, teachers or research workers in Internal Medicine or in an allied specialty, etc." It was proposed to leave out the phrase, "or in an allied specialty," thus restricting future membership to those engaged in Internal Medicine alone. It was also proposed to make the successful passage of the examination for certification a pre-requisite for Associateship. These changes if adopted, while in no way affecting our present membership, would have influenced materially the future selection of Associates and Fellows. At the meeting of the Board of Regents last Sunday it was decided not to take up consideration of these amendments at this time.

It is apparent that Fellowship in the College will mean much more than mere Certification, which is only one qualification that must be met, just as it is necessary now that the candidate be a graduate of an approved medical school and must hold membership in his county, state and national medical organizations. These are preliminary requirements. Many other qualifications for Fellowship are now considered by the Committee on Credentials, and as time goes on Fellowship will become more difficult and therefore more desirable than in the past.

Two years ago it seemed apparent to the Officers and Regents of our College that a Board for the Certification of Internists would be formed, and it was felt that if such were the case the American College of Physicians should exercise control over it. Since the American Board of Ophthalmology was formed twenty-four years ago and eight other boards were organized prior to the American Board of Internal Medicine, it must be evident that this procedure was not entered into hastily. The personnel of the American Board of Internal Medicine is a sufficient guarantee of its

successful administration The College owes a great debt to the Chairman and members of this Board for the time and energy which they have spent in this very complicated organization The Chairman, Dr Walter L Bierring, will discuss more fully the workings of this Board at the General Sessions

The other most interesting achievement of the College during the past year was the purchase of a building in Philadelphia as a permanent home Encouraged by my predecessor, Dr James Alexander Miller, the pioneer work on this project was done by Dr Alfred Stengel prior to our meeting in Detroit last year Their arguments convinced the Boards of Regents and Governors that the College should own a suitable headquarters building It no longer seemed appropriate that an organization of our size and importance should occupy rented rooms in an office building Accordingly, a Committee on College Headquarters was appointed, which after much investigation, advised the purchase of a fine old residence in Philadelphia This purchase was consummated during the past summer, a few necessary alterations were made and the house was furnished in time for the December meeting of the Board of Regents The thanks of the College for the selection of the property and for the successful completion of this project should be tendered to this committee, of which Dr O H Perry Pepper was Chairman Fortunately for us, large city houses of this sort are not in great demand, so that the College was able to acquire a very handsome and expensive property at very little more than the value of the lot upon which it stands It is situated on the corner of Pine and Forty-Second Streets in Philadelphia in a neighborhood that apparently will not soon deteriorate The house is a three-story brick residence, dignified in appearance, and is surrounded by a large yard with beautiful planting The whole property is enclosed by a high iron fence which adds much to its appearance The advantages of this acquisition are that the executive offices now have abundant space, there are rooms for the meetings of the Board of Regents and their committees, further expansion is provided for when it becomes necessary, and the College has a home of its own of which I am sure you will be proud All members are urged to visit the new headquarters when in Philadelphia

One of the encouraging features of the past year has been the increased interest shown in Life Memberships As you know, the revenue from this source goes into the endowment fund, the income from which is used solely to further the scientific purposes of the College In the year just closed 18 Fellows have shown concretely that they appreciate this aim of the College We now have a total of 79 Life Members and about \$62,000 00 in this fund

Numerically, the membership of the College has shown a healthy growth during the year One hundred and seventy-two have been elected to Fellowship and 276 to Associateship On the roster of the College at the present time there are 2 Masters, 2684 Fellows and 998 Associates, a total of 3684

This is a large number and results in such a big attendance at these Annual Sessions that only the largest cities can adequately care for them. However, with the standards for membership being constantly made more rigid, the growth of the College will necessarily be much slower from this time forward, and from a practical standpoint this is not an unmixed evil. The meetings would lose much if they should have to be divided into Regional Assemblies, as is done by another of our national societies.

Detracting in no way from these Annual Sessions have been the state meetings which have shown a remarkable increase in the past two years due to the efforts of our Governors. These state meetings have been more or less social. Some have been held at the time and place of the meeting of the State Medical Society, while others have convened at some central city with or without a scientific program. It has been my good fortune during the past year to attend several of these state gatherings, and at all of them, those in attendance seemed enthusiastic and voted to continue these meetings annually.

After discussing the growth of the College, it is fitting that we now take account of our losses since our last meeting. For failure to pay dues or by resignation we have lost only 10 Fellows and 10 Associates. Death, however, has not been so kind. Two Masters, 52 Fellows and 4 Associates have passed to the "great beyond." Included in this list were some of our most active and distinguished members. Time will permit me to refer to only a few—Henry F. Stoll and Ernest E. Laubaugh, Governors for the States of Connecticut and Idaho respectively, and Luther F. Warren of Brooklyn, a member of the Board of Regents, were actively engaged in the affairs of the College and will be sorely missed. W. McKim Marriott and Henry S. Plummer were former members of the Board of Regents. Both of these men were known personally or by reputation to all of you. Dr. Marriott, as you know, had recently removed from this city to San Francisco. Dr. Plummer's work at the Mayo Clinic is equally well-known to you. It would be futile for me to enumerate the professional attainments of these eminent physicians. Their work is familiar to the whole medical world.

We mourn also tonight three past presidents, James M. Anders, Harlow Brooks and Frank Smithies. James M. Anders, called the "Nestor of the Philadelphia Medical Profession," "A Gentleman of the Old School," was President of the College in 1922 to 1923 and was the first to be honored with the title of "Master of the American College of Physicians." He was known to all internists in America, and was the author of many medical works. He maintained a lively interest in this society until the time of his death.

Harlow Brooks of New York, was President for the two years succeeding Dr. Anders, 1923 to 1925 and was a member of the Board of Regents for a number of years. He became a Fellow in 1916 at the first regular

meeting of the College and also served as Governor of the College for New York from 1929 to 1931. He has been called the "Doctor's Doctor," had a nation-wide reputation as a diagnostician and was widely sought as a consultant. He was loved by all who knew him well.

Frank Smithies, whose death occurred rather suddenly early in February, deserves especial mention. If it had not been for Frank Smithies there might not have been an American College of Physicians, at any rate, he had much to do with its formation. During its early years *he* was the College. He arranged the places of meeting, made out the programs and carried on practically all the business of the College. He was the founder of our Journal. He was Secretary-General from 1922 to 1926 and President 1927 to 1928. In recognition of his work he was made a "Master." Frank Smithies had great personality, he possessed an almost unbelievable capacity for hard work, which in spite of physical handicaps enabled him to win distinction and many honors in the field of American Medicine. In the passing of James M. Anders, Harlow Brooks and Frank Smithies, the College has lost three of its pioneers, who served it in its infancy.

The College is an infant no longer. This year marks the twenty-first Annual Sessions, so that now it may be said to be grown to manhood, and like a young man, it is strong, virile, optimistic and progressive. During these twenty-one years it has gradually attained all the objectives for which these pioneer founders had hoped. The Annual Sessions still remain its most important accomplishment, but other activities, most of which I have mentioned, are hardly less valuable. Through the establishment of the John Phillips Memorial Award and the giving of Fellowships to assist in research work, it recognizes and aids the efforts of earnest students of medicine. It owns and publishes a great medical journal. Furthermore, it is supervising the classification and certification of Internists. And it now owns a permanent home. These results, while gratifying, are not enough. We must not allow ourselves to become satisfied. Dr. Aldred Scott Warthin pointed out in an Editorial a short time before his death, that the College must develop its cultural side and take advantage of its opportunities to influence and guide medical thought in the country. I feel that now, given the right kind of leadership, with our strong organization, the College may look forward to the future with eagerness and confidence, and that it will do its part toward the forming of medical ideals throughout America.

THE AMERICAN BOARD OF INTERNAL MEDICINE *

By WALTER L. BIERRING, M D , F A C P , Chairman, *Des Moines, Iowa*

THE growth of specialism in America is in line with progress, and significant of the remarkable advancement of knowledge in every field of medicine since the opening of the century

That modern diagnostic technic is based on special training is obvious, and its influence towards specialized medical and surgical practice is likewise apparent

In the evolution of American medical schools during the past three decades, uniformity of curriculum and hours of study constituted all too frequently the principal standard of measurement, and in consequence, courses in certain specialties occupied a large part of the undergraduate curriculum

This was reflected in the increasing number of medical graduates taking up one or the other of the specialties, directly upon admission to practice. The studies of Weiskotten indicated that an average of 10 per cent of recent graduates entered the field of specialized practice in 1910, and this rose to the unusual figure of 35 per cent in 1930. This state of affairs became a matter of considerable concern to medical educators, and the profession generally recognized the inherent dangers of this large influx of incompletely prepared specialists in the different fields.

With the advent of special certification, the training of specialists is definitely within the field of postgraduate medical education.

In certain of the European countries legal provisions control the licensure of specialists, but such measures did not seem practicable for this country. In the many discussions on the subject, the consensus was that the responsibility lay on the organized medical profession as represented by the American Medical Association, and that any form of legislative control was undesirable.

It is to the credit of special societies in two specialties, ophthalmology and otolaryngology, that they have taken the initiative and led the way towards the formation of qualifying and certifying boards in the different medical specialties.

The American Board of Ophthalmology was the pioneer in this field, being organized in 1916, and has been certifying specialists in ophthalmology ever since. The American Board of Otolaryngology was formed in 1923, the American Board of Obstetrics and Gynecology in 1927, and the American Board of Dermatology and Syphilology in 1929.

As other specialties began to take steps towards forming similar qualifying boards, the need was recognized for some central agency or supervising

* Presented at the St. Louis meeting of the American College of Physicians, April 22, 1937.

body such as the Council on Medical Education and Hospitals of the American Medical Association for the purpose of coordinating graduate education and the certification of specialists in the United States and Canada. A further purpose was to formulate standards of administration in general, based upon those of the four specialty boards previously organized, and to recognize new boards meeting those standards.

In order to avoid duplication of effort as well as to coordinate the work of the several boards, and other interested groups, it was deemed advisable to create an Advisory Board for Medical Specialties, which should be representative of each organization concerned. This Advisory Board began to function in February 1934. Since that time the American Board of Pediatrics, the American Board of Neurology and Psychiatry, the American Board of Radiology, the American Board of Orthopedic Surgery, the American Board of Urology, the American Board of Internal Medicine, the American Board of Pathology, and the American Board of Surgery have been formed, thus completing the organization of certifying boards in the twelve recognized medical and surgical specialties.

Each of the twelve specialty boards comprise in their membership representatives from the national special societies concerned and the section of the particular specialty in the Scientific Assembly of the American Medical Association.

The formation of an American Board for the Certification of Internists originated with the action of the Board of Regents of the American College of Physicians at the session in Philadelphia, April 30, 1935, when a resolution was adopted to cooperate with the Section on the Practice of Medicine of the American Medical Association in the appointment of a representative committee of organization.

After fulfilling the necessary requirements to obtain the approval of the Advisory Board for Medical Specialties and the Council on Medical Education and Hospitals of the American Medical Association, the Articles of Incorporation of the American Board of Internal Medicine were filed on the twenty-eighth day of February 1936.

The official organization was completed and the Board began to function on July 1, 1936. The membership of the first Board was composed of the following members: Dr. Jonathan C. Meakins, Montreal, Vice-Chairman, Dr. O. H. Perry Pepper, Philadelphia, Secretary-Treasurer, Dr. David P. Barr, St. Louis, Dr. William S. Middleton, Madison, Wisconsin, and Dr. G. Gill Richards, Salt Lake City, representing the American College of Physicians, and Dr. Ernest E. Irons, Chicago, Dr. Reginald Fitz, Boston, Dr. John H. Musser, New Orleans, and Dr. Walter L. Bierring, Des Moines, Chairman, as representatives of the Section on the Practice of Medicine of the American Medical Association.

The purpose and objective of the Board is the certification of specialists in the field of internal medicine, and the establishment of qualifications for

such certification, and of the procedure necessary for the accomplishment of such objective

In its various announcements, the Board has endeavored not to establish any fixed rules for the preliminary training of candidates for certification in this field, but rather to outline or suggest certain broad general principles for training—subject by necessity, to constant changes reflecting the dynamic nature of the specialty

It is generally recognized that a sound knowledge of physiology, biochemistry, pathology and the other basic sciences, insofar as they apply to disease, is essential for continued progress of the individual who practices internal medicine

A portion of the written examination required for certification is, therefore, designed to test the candidates' knowledge of these "pre-clinical" subjects and especially in their application to disease rather than their purely laboratory aspects

The mere factual knowledge of medicine and its basic sciences is not sufficient. The candidate must have had training in their use in furthering his understanding in clinical medicine. This implies practical experience under the guidance of older men who bring to their clinical problems ripe knowledge and critical judgment. Preparation to meet this requirement adequately may be even more difficult to obtain than the so-called scientific training. It may, however, be acquired in the following ways

- A By work in a well-organized hospital out-door clinic conducted by competent physicians
- B By a prolonged period of resident hospital appointments, likewise directed by skilled physicians
- C By a period of training in intimate association with a well-trained and critical physician who takes the trouble to teach and guide his assistant rather than to expect him only to carry out the minor drudgery of a busy practice

The Board does not consider it to the best interests of internal medicine in this country that rigid rules as to where or how the training outlined above is to be obtained. Medical teaching and knowledge are international. The opportunities of all prospective candidates are not the same. Some may have the opportunity of widening their knowledge by a period of study abroad. Others, at the other extreme, may be restricted to a comparatively narrow geographic area and their more detailed training must be obtained in short periods scattered over a longer period of time. Although it is required that at least five years must elapse between the termination of the first intern year and the date when the candidate is eligible to take the examination, a longer period is advisable. The Board wishes to emphasize that time and training are but a means to the end of acquiring a breadth and depth of knowledge of internal medicine which the candidate must demonstrate to the Board in order to justify it in certifying that he is competent to

practice internal medicine as a specialty. The responsibility of acquiring the knowledge as best he may rests with the candidate, while the responsibility of maintaining the standard of knowledge required for certification devolves on the Board.

The examination required of candidates for certification as specialists in internal medicine will consist of Part I (written), and Part II (practical or clinical).

Part I. The written examination is to be held simultaneously in different sections of the United States and Canada and will include

- A. Questions in applied physiology, anatomy, physiological chemistry, pathology, bacteriology, and pharmacology as related to internal medicine as well as the cultural aspects of medicine.
- B. Questions in general internal medicine.

Part II. Candidates successful in the written tests will be eligible for the practical or clinical examination, which will be conducted by the members of the Board near the time and place of the annual meeting of the American College of Physicians and of the American Medical Association.

Two written examinations have been held, with fifty (50) candidates appearing for the examination on December 14, 1936 and thirty-six (36) on March 22, 1937.

The first practical examination will be conducted by members of the Board at the City Hospital, St. Louis, on April 23, 1937, at which thirty-five (35) candidates are expected to appear. A second practical examination will be conducted in Philadelphia on June 5, 1937. The next written test will be held in different centers in October 1937 and a practical examination will be held in Chicago in February 1937.

CERTIFICATION WITHOUT EXAMINATION

The organization, during the past forty years, of seven special societies concerned mainly with the advancement of internal medicine is significant of the leadership that has been attained in this specialized form of medical practice.

The desire to maintain these high standards of internal medicine has been a potent influence in developing the present plan of certification procedure.

In inaugurating this movement it seemed fitting to consider the special recognition of leading internists in the United States and Canada, who as teachers or through experience in specialized practice had distinctly contributed to the advancement of internal medicine.

It was therefore decided to consider applications for certification without examination from the following three groups:

- 1 Professors and associate professors of medicine in approved medical schools in United States and Canada
- 2 Members or Fellows in good standing in the following special societies, who had limited their practice to the specialty of internal medicine for ten years or longer
 - A* Association of American Physicians
 - B* American College of Physicians
 - C* Royal College of Physicians of Canada
 - D* American Clinical and Climatological Association
 - E* American Gastro-Enterological Association
 - F* American Society for Clinical Investigation
 - G* Central Society for Clinical Research
- 3 Licensed physicians who had limited their practice to the specialty of internal medicine for fifteen (15) years or longer and were recommended for certification by the Executive Committee of the Section on the Practice of Medicine of the American Medical Association

During the year more than one thousand (1000) of such applications have been received and the proper evaluation of the eligibility of each applicant has proved a more difficult problem than at first anticipated. As several months will probably transpire before final announcement can be made, the Board trusts that it may enlist the charity and patience of all those who are concerned.

The certification of the more limited specialties of internal medicine such as cardiology, gastro-enterology, allergy, tuberculosis, etc., has been given very careful consideration by the Board since its organization.

In an earlier announcement the Board published the intention to inaugurate, immediately after July 1, 1937, qualification and procedure similar to that in general internal medicine, for additional certification in the above named restricted and specialized branches.

In view of the various problems that have developed during the period of organization and institution of the general plan of certifying procedure, the Board considers that it would be more practical to defer this additional certification for the present or until the plan of certification of specialists in the general field of internal medicine is more completely established.

The general approval that has been accorded the American Board of Internal Medicine in its efforts to institute the aims and purposes for which it was organized has been most gratifying. The Board takes this opportunity to express its obligation to the Officers, Regents, Governors and Fellows of the American College of Physicians, as well as to the members of the Executive Committee of the Section on the Practice of Medicine of the American Medical Association and the officers of the several special societies of internal medicine for valuable advice and counsel extended at all times.

The Board trusts that it can continue to count on this cooperation, particularly in directing the younger physicians in courses of special training with certification in internal medicine as the objective

It will be evident that the standard of qualifications for election to Fellowship in the American College of Physicians and in other special societies of internal medicine will be distinctly influenced by such certification

The Board is, likewise, firmly convinced that the simple procedure of certification is of minor import as compared with the effect this movement will have in elevating the standards of medical specialists, in advancing the development of postgraduate medical education, particularly the thorough training in internal medicine, and ultimately in benefiting the patient who is at all times entitled to the highest type of medical service

RHEUMATIC HEART DISEASE IN PHILADELPHIA SCHOOL CHILDREN¹

By JACOB M. CAHAN, M.D., F.A.C.P., *Philadelphia, Pennsylvania*

ABOUT 1 per cent of the 350,000 children in the public and parochial schools of Philadelphia[†] have some form of heart disease. The main causes of heart affection, as is well known, are congenital developmental defects, rheumatic fever and other infections, syphilis and degenerative changes. Of these causes, congenital defects and rheumatic infection, chiefly, pertain to children of school age, and rheumatic heart disease by itself constitutes by far the most frequent variety. The common age at the onset of rheumatic infection coincides with the years of the child's school attendance, namely, from five to eighteen. In fact, the child is most susceptible to rheumatic infection during the first four years of school attendance. The opportunity to study the earliest phenomena of the greatest cause of heart disease in children thus presents itself to the medical supervisor of the pupils' health.

PROSPECTUS OF THE REPORT

Briefly outlined, this report contains the following:

- 1 Inferences that can be drawn from the histories of juvenile rheumatic infection
- 2 Prevalence of various infections in the children studied
- 3 The incidence of abnormal hearts
- 4 The incidence of recognizable congenital and rheumatic heart disease
- 5 Classification and description of restrictions of physical activities in public schools
- 6 Correlation of the functional capacity of the cardiac patient with the restricted physical activities
- 7 Diagnostic aids in determining when the rheumatic infection is inactive
- 8 A word as to how safely a child with heart disease can be guided through his school years

PROCEDURE

Eleven public school physicians reviewed the medical record cards[‡] of 33,293 pupils enrolled in one school district, known as District No. 9. These medical records showed the respective school physician's findings at

* Received for publication August 12, 1936.

† Philadelphia, Pennsylvania, is a city of over two million inhabitants, and has a temperate climate. North Philadelphia, the section in which the survey has been conducted, is inhabited largely by families whose social condition is a little better than the average, although about one-fifth of them are poor.

‡ A blank form will be furnished with the reprint, on request.

the annual physical examination of the pupil. Thus, unlike a previous survey¹ based on my own selection, these children have been nominated for study by the 11 medical inspectors in the schools. Of the many items found on a pupil's medical record, the following were selected: name, school, date of birth, sex, race, and grade. In addition, for each pupil a note was made of the date of the physical examination that indicated the abnormal cardiac condition, the diagnosis made or signs discovered on examination of the heart, the severity of the condition, whether the pupil had been indulging in gymnasium work, any other defect that had been discovered, and the identification number of the school physician. A notation was made of every child who had any abnormality marked under the caption of "heart," at any previous examination. Any record of "nervousness" and "chorea" was also noted. Another source of suspected heart cases was found in prolonged absences, recorded with the Compulsory Attendance Department. The Compulsory Department supervises prolonged absences, and enforces attendance. Children who are unable to attend school furnish the school which they should attend with an excuse from their private physician or report from hospital. The Compulsory Department, in the district surveyed, had on file reports on 261 children who had been absent for months or years. Twenty-four of these reports (9 per cent) showed the absences to be due to some circulatory disturbance, and these cases were included in the study. Additional names of suspected heart cases were obtained from the 28 school principals, their secretaries, and the 11 school nurses employed in this district. While there are 10 school districts in the city, the survey covered about one-eighth of the entire public school population, and about one-ninth of all the Philadelphia children of school age.

A preliminary physical examination was the next step. Of the 863 pupils examined the first time, 472 showed no evidence of heart lesion or suspicion of it, and were thus eliminated, and 391 were slated for study. A juvenile rheumatic disease blank was then provided for each case, and the history was obtained from the parent, by a school nurse or physician. For the girls, a special permission was secured to remove "sufficient clothing from the chest and shoulders" to enable the doctor to examine the chest carefully.

The physical examination of the children included mainly the parts of the body bearing on the circulatory system. An attempt was made, however, to investigate any additional points of interest, disclosed in the anamnesis or by signs revealed on examination. In all cases reexaminations were made within the next year, and in many instances a third examination was made this year, 1936.

INFERENCES FROM THE HISTORIES

Each summarized history was placed in one of three different classes, depending on the amount and nature of evidence of rheumatic infection,

namely "Actual," when acute rheumatic fever, chorea, or other unmistakable history of rheumatic infection was present, "Suspicious," when there was no convincing proof of actual infection, and "Negative," when there was no past or present evidence of rheumatic affection. A tabulation of all items in these histories showed tens of thousands of entries, a discussion of which would be too lengthy. Nor is it necessary. A brief comment on some of the more interesting points will suffice.

The particular school population of 33,293 pupils surveyed contained 157 children of the negro race, but of the 391 cases studied, only one was colored. Of these 391 studied cases, 214 were boys and 177 girls. Three hundred and fifty of the 391 studied showed abnormalities, either in the history or on physical examination, or in both. Of these 350 (1.1 per cent of entire school population reviewed), 191 (0.6 per cent) showed signs of organic heart disease, later to be described, 113 (0.33 per cent) pupils were recorded as showing "Abnormal signs or symptoms referable to the heart but the diagnosis of heart disease uncertain" (Class E), and 46 (0.013 per cent) were classed as children "Without circulatory disease whom it is advisable to follow because of the presence or history of an etiological factor which might cause heart disease" (Class F). These two classes and their quoted definitions are in compliance with the Standard Classification and Diagnosis of Heart Disease as accepted by the American Heart Association.

Classes E and F should form interesting groups for observation, prolonged if possible, even after the pupils leave the public school. Will they establish their freedom from heart affection, retain their functional heart conditions, or develop organic heart disease? If the last should happen, one would like to know under what circumstances it has occurred, and if it was possible to prevent it.

It is interesting to note that in the final classification eight children with organic heart disease had entirely negative histories as far as any infection allied to juvenile rheumatic disease, or known congenital maldevelopment is concerned. On the other hand, five pupils with actual histories of past rheumatic infection, 45 with suspicious histories, and 63 with negative histories were among those children in Class E. Five children with actual histories, 19 with suspicious histories, and 22 with negative histories belonged to Class F. Thus, it is quite possible that, had histories been obtained on all 863 nominated pupils, and had the 472 children not been entirely eliminated at the first examination that additional children with heart disease would have been discovered. Also, more children might have been found belonging to Class E or F.

In the subsequent discussions of points in the anamnesis, the numbers and percentages refer to the 350 pupils with abnormal hearts. Children belonging to Classes E and F have been included in this discussion.

DISCUSSION OF SOME MANIFESTATIONS

Tonsillitis Of the 140 children (40 per cent) that had tonsillitis, 61 had an occasional attack, 53 had few attacks, 21 had many attacks, and 5 had very many attacks. The total number of children that had tonsillitis at the ages of three, five, and six, was one and one-half times the total number of cases of all the children of all other ages between two and fourteen. In fact, almost one-half of all the children that had tonsillitis had their first attacks at the ages of five and six. Within a year of the first attack of tonsillitis, 43 children had their tonsils removed, and before two years passed, 37 more had the operation. Altogether 101 children who had had tonsillitis subsequently had tonsillectomies, but there were 11 additional children who gave a history of tonsillitis after tonsillectomy. A total of 110 children had no history of tonsillitis yet had tonsillectomies, and only 28 that had had tonsillitis had no tonsillectomies. Of the 65 children that had acute rheumatic fever, 36 had tonsillectomies before the first attack of rheumatic fever, 15 after it, and 14 children had no tonsillectomies. Of the 39 pupils that had chorea, 15 had their first attack before tonsillectomy, 17 had it after the operation, while seven had retained their tonsils. One can infer from these data, among other things, that the popular operation of tonsillectomy is often inadequate to prevent entirely or to ameliorate without fail all cases of chorea, acute rheumatic fever or rheumatic heart disease. Even tonsillitis itself had occurred after some tonsillectomies.

Acute rheumatic fever was present in 18.6 per cent of the histories. More children had their first acute attack of rheumatic fever, *recurrent fever*, and *involuntary twitchings* at the age of seven than at any other age. The number of attacks of rheumatic fever varied from one to five, the last mentioned being in a child whose first attack occurred at seven.

Chorea occurred in 11 per cent. The first attack of chorea occurred in more children at eight years of age than at any other age. At the ages of seven and five the next larger number of children had their first attack.

A greater number of children had their first or only attack of *recurrent unexplained abdominal pains*, *joint pains*, *swelling of joints*, *pain in the region of the heart*, "*heart disease*," and *scarlet fever* at five years than at any other age.

Emmesis occurred for the first time most frequently in children of nine years, *severe muscle* or "*growing pains*," at 10 years of age, and "*heart failure*" at eleven. An equal number of children had their first attack of epistaxis at eight and 12 years of age. The onset of *sinus disease* was noted most frequently in the twelfth year, although it began almost as frequently in the third and sixth years. Dental infection was present in 52 per cent of the children.

Familial Predisposition The insidiousness of the onset of many cases of rheumatic heart disease and the chronicity of the asymptomatic stage of the heart affection make one suspect the possibility of familial incidence of

the disease, as in tuberculosis. This was borne out in this survey. Among the 350 cardiacs 79 (22.6 per cent) had a history either of some near relative having heart affection or of a sibling with rheumatic heart disease. These relatives were as follows: 29 grandparents, 20 mothers, three fathers, both parents (one instance), other relatives (eight instances), nine brothers and nine sisters. Four pairs of siblings were under observation. Unfortunately, it was not ascertained whether among the adults there were some suffering from other than rheumatic heart disease—which was very likely. In view of this incidence of rheumatic heart disease in the family, examination of every available member of the family is advisable, once a member is found to have rheumatic heart disease.

A brief summary of the actual, suspicious and negative histories of the 391 cardiac suspects is shown in the following table.

TABLE I
Prevalence of Conditions in 391 Histories

Conditions in order of prevalence	In children with			Total
	Actual rheumatic history	Suspicious rheumatic history	Negative history	
Measles	80	116	121	317
Pertussis	59	70	76	205
Tonsillitis	44	62	34	140
"Heart disease"	57	54	24	135
Severe muscle or "growing pains"	38	58	16	112
Recurrent common colds	25	37	21	83
Heart pains	33	46	4	83
Chicken pox	27	20	20	67
Acute rheumatic fever	58	7	0	65
Scarlet fever	21	29	10	60
Recurrent unexplained abdominal pains	21	35	2	58
Pneumonia	13	22	20	55
Involuntary twitchings	35	16	4	55
Joint pains	29	24	1	54
Epistaxis	20	16	12	48
Recurrent fever	24	14	3	41
Mumps	18	13	10	41
Chorea	38	1	0	39
Enuresis	10	19	9	38
Diphtheria	8	17	10	35
Influenza	12	15	3	30
Swelling of joints	17	4	1	22
Sinus disease	4	11	6	21
"Heart failure"	8	8	4	20
Nodules under the skin	2	1	0	3

PHYSICAL EXAMINATIONS

Mindful of the inference drawn from the history, each girl as well as boy was examined with bared front of the chest. There were just as many pupils with rheumatic cardiac affection whose general appearance was fair or good as there were of poor appearance. Twenty-one showed choreiform

movements. Pallor and fever were found in a smaller percentage of children examined in school than in those examined at home. Tonsils were present in almost 50 per cent of the children. Two-thirds of the children had enlarged glands in the neck. A pulse rate of over 100 per minute was not found indicative of rheumatic affection, as many children without signs of heart disease also had that rate. The temperatures of a number of children were above 99° F (by mouth). For the sake of brevity, diagnoses will be stated without enumerating the accepted diagnostic signs or criteria. I wish to introduce and discuss, however, a new anatomical landmark used for the anterior chest wall.

A NEW LANDMARK ON THE CHEST WALL

In recording cardiac enlargement I have been in the habit of designating the point midway between the midclavicular and anterior axillary lines as the "preaxillary" line, adding the interspace at which the apex beat was felt. The preaxillary line is an imaginary line on the front of either side of the chest, drawn vertically downward, midway between the midclavicular and anterior axillary lines, and parallel to them. It divides vertically the surface area of the chest wall between the midclavicular and anterior axillary lines exactly in half. Unlike the parasternal line which is similarly drawn from the medial half of the clavicle, the preaxillary line does not take origin from the outer half of the clavicle. Although I do not remember seeing any reference to such an anatomical landmark, I find it more convenient and descriptive than any measured distance from the midclavicular line. The preaxillary line seems to me to have a more constant relation to the person's chest as it is applicable to a patient of any age, size, or stature. Furthermore, one can express the relation of the apex beat to the preaxillary line by stating whether the apex beat is near or beyond this line. The apex beat may be located midway between the midclavicular and preaxillary lines or between the preaxillary and anterior axillary lines. Such a descriptive location of the apex beat seems to make possible a more constant anatomical site of the finding. A given measured distance in centimeters or inches would not be so self-explanatory, for one must know the approximate size of the chest. What is true of the use of the preaxillary line for the apex beat is also true for designating the margin of cardiac dullness, and flatness of pericardial effusion. Less frequently, the preaxillary line on either side may be used to designate the outline of pathologic pulmonary or pleuritic structures, as in extracardiac foreign bodies, consolidations, effusions or neoplasm in the chest.

DIAGNOSES OF HEART DISEASE

A diagnosis of organic heart disease, congenital or acquired, was made in 191 pupils. Briefly, the diagnoses were as follows:

<i>Etiological Diagnosis</i>	No. of Cases
Congenital developmental defect	28
Congenital developmental defect combined with acquired heart disease, rheumatic	2
Rheumatic heart disease, active and inactive	129
Measles	1
Scarlet fever	8
Hypertension	4
Nephritis	1
Unknown (probably rheumatic)	18
Total	191

Anatomical Diagnosis

Congenital cyanotic lesion (tetralogy of Fallot)	4
Congenital acyanotic lesion	24
Hypertrophy of heart, including 3 cases with chronic adhesive pericarditis	44
Cardiac valvular disease, including 2 having also congenital acyanotic lesions	118
Aortic insufficiency, including 1 with chronic adhesive pericarditis	8
Double aortic lesion	1
Aortic insufficiency and double mitral	1
Double aortic and double mitral	1
Mitral insufficiency	42
Mitral stenosis	21
Double mitral	44
Aortitis	1
Total	191

Physiological Diagnosis Disregarding sinus arrhythmia, which is found both in normal children and in children with heart disease, four pupils showed pathologic conduction systems, as follows: two had heart blocks, one had left and right premature ventricular beats with some intraventricular conduction delay, and one had premature contractions of which the point of origin remained unknown, as there was no opportunity for electrocardiographic study.

The *Functional Classification* varied in a number of children during the period of observation, but on the average, the cardiac capacity for exertion was as follows:

	No. of Cases	Per Cent
Class 1	131	68.6
Class 2a	41	21.5
Class 2b	15	7.9
Class 3	4	2.1

TABLE II

Heart Conditions in School Children Surveyed

Total number of pupils' medical records reviewed 33,293

	Number of children	Per cent
Pupils with suspected cardiac abnormality nominated by school physicians for study	863	2.6
Pupils for whom medical histories were obtained	391	1.14
Abnormal symptoms or signs relative to the heart were found in	350	1.05
Organic heart disease	191	0.6
Congenital heart disease (including two having also acquired lesions)	30	0.09
Acquired heart disease	161	0.5
Class E	113	0.33
Class F	46	0.13
No heart abnormality	41	

When the school population was divided into the younger and older children, or elementary and high school pupils, the respective enrollments and incidence of heart abnormalities found were as follows:

TABLE III
Heart Abnormalities in Younger and Older Children

	Elementary school (ages 6-14 years)		High school (ages 15-18 years)		Total	
No of pupils on roll	24,193		9,154		33,293	
	No	Per cent	No	Per cent	No	Per cent
Organic heart disease	111	0 5	80	0 9	191	0 6
Class E	74	0 3	39	0 4	113	0 33
Class F	30	0 12	16	0 2	46	0 13
Total abnormal hearts	215	0 9	135	1 5	350	1 1

RESTRICTION OF PHYSICAL ACTIVITIES

To insure the teacher's cooperation in restriction of the pupil's physical activities in school, the physician treating the child certifies on a blank form as to the duration and the cause of the excuse from exercises. The school physician may act for the family doctor. In either case, the certificate may be honored for 1, 2, or 3 months, and has to be renewed thereafter, unless it is endorsed by the medical supervisor. The supervisor has the authority to approve the certificate for a longer period of time, or even for the duration of the pupil's entire school life. In addition to the cause and duration of the restriction of physical activities, the exercises allowed are indicated and checked on the certificate as follows:

- 1 Competitive sports, requiring considerable exertion
- 2 Vigorous exercises on gymnasium apparatus. Running and jumping
- 3 Calisthenics and general exercises, simple games and play. These activities require little running or muscular effort
- 4 Very mild exercises (movements of arms, legs, neck and trunk)—duration 10 minutes
- 5 Very mild exercises (movements of arms, legs, neck and trunk)—duration five minutes

These listed physical activities are not descriptive of the degree of exertion required. I have therefore secured from the director of physical and health education, Mr. Grover W. Mueller, an interpretation of the classifications which appear on the certificate. The numbered physical activities are briefly described by Mr. Mueller, as follows:

INTERPRETATION OF CLASSIFICATIONS OF RESTRICTION OF PHYSICAL ACTIVITIES

- 1 Football, basketball, soccer, track and field events, lacrosse, field hockey, ice hockey, wrestling, boxing, competitive swimming, etc. These activities are characterized by vigorous activity, many moments of minimum effort, and many instances of sustained effort. The competitive element stimulates continuation of effort and participation which in the absence of such stimulus would be interrupted by intervals

of rest or relative inactivity. Speed, endurance, effort, and skill are the main physical qualities involved. Stimulation of the emotions and of the circulatory and respiratory systems is pronounced.

2 Vigorous exercises on the parallel and horizontal bars, rings, horse, buck and mats, hopping and jumping, vigorous dancing, such as folk dancing, non-competitive running, except that the running often is a part of competitive games of low organization, thus often resulting in vigorous running. The activities on the apparatus are characterized by the physical qualities of strength and skill, the running, hopping, and jumping are characterized by stimulation of the circulatory and respiratory systems. Great momentary effort frequently occurs, but effort is not sustained for more than a few moments and stimulation is not nearly so great as in Group 1. Emotional stimulation is slight.

3 General free exercises (calisthenics), mild forms of dancing, mild exercises on apparatus which are done in hanging and sitting positions, simple games and play. These activities involve mild contraction and extension of most of the muscle groups. The activity is alternated with regular short intervals of rest, effort is neither great nor sustained, there is only slight physiological stimulation, strength is involved only momentarily and in slight degree, skill is involved, consisting mainly of hand, arm, and eye coordination. Running is either in one spot or over short distances at moderate speed. The competitive element is lacking entirely, and no emotional stimulus is involved.

4 General free exercises (calisthenics) and simple play forms. These free exercises involve very mild contraction and extension of most of the muscle groups. They differ from those in Group 3 in that the exercises are more localized, they are not repeated so often, the intervals of rest are more frequent and of longer duration, and many of the exercises are done in the sitting and lying positions. Pupils may stop at any time they feel tired. Some exercises are done against mild resistance set up by a second person. The play forms involve little effort and consist almost entirely of hand, arm, and eye coordination, such as throwing rubber quoits, and throwing a ball over a short distance at a goal. In none of these exercises is strength involved except in the mildest possible degree. Running, hopping and jumping as well as any other activity which stimulates the circulatory and respiratory systems in any but the mildest degree are omitted entirely.

5 The activities in this group are identical with those in Group 4. The difference in the two groups is entirely in the total amount of physical work done. In Group 5 half as much work is done in one-half as much time (5 minutes) as in Group 4 (10 minutes).

Depending on the degree of the pupil's handicap there are four more listed "physical activities" each requiring less and less energy in successive degrees.

6 Walking only—10 minutes

7 No exercise, but ordinary activity throughout the school day

8 No exercise. Full day attendance. Rest during recess period. Pupil is allowed to move from room to room and to use stairs without regard to movement of classmates. Use of school elevator if there is one.

9 No exercise. Same privileges as number 8. Pupil is allowed to stay home in the afternoon to rest, whenever necessary.

The above classification of restrictions of physical activities has a definite relation to a pupil's physical capacity for exertion. It may be well therefore, to recollect at this time the standard classification of Functional Capacity

approved by the American Heart Association, and later discuss the application in school of the classification of restricted physical activities to the given functional capacity of the pupil with heart disease. The two together will permit a better correlation between the pupil's routine in the school and the cardiac capacity for exertion.

FUNCTIONAL CLASSIFICATION OF PATIENTS WITH ORGANIC HEART DISEASE

Class 1 Patients with organic heart disease, able to carry on ordinary physical activity without discomfort

Class 2 Patients with organic heart disease, unable to carry on ordinary physical activity without discomfort

a Activity slightly limited

b Activity greatly limited

Class 3 Patients with organic heart disease and with symptoms or signs of heart failure when at rest, unable to carry on any physical activity without discomfort

CORRELATION OF FUNCTIONAL CAPACITY WITH RESTRICTIONS OF PHYSICAL ACTIVITIES

I am frequently faced with the problem of correlating the functional capacity of the child with heart disease with the restriction of physical activities in the school. At times I am asked to endorse the family physician's request for the same. Children have to be guarded against participating in physical exercises to a prohibitive degree and against failing to indulge in permissible activities. The former may aggravate the cardiac condition or, through fatigue, lead to serious accidents, while the latter deprives the pupil of a necessary amount of physical culture and scholastic development. As a rule, though, it is safe to assume that the average child with heart disease will do all he can. Only in rare instances, as in the child who is not proficient in the activity, will he attempt to dodge the gymnastic requirement of the curriculum. Although a child with a Functional Capacity of Class 1, for instance, can usually be as active as any child that has no heart disease, it is not advisable to permit him to indulge in competitive sports which may over-stimulate activity beyond his endurance. Rather, it seems to me, the pupil should indulge in physical activities to a moderate degree that will satisfy his desire for athletics, and yet avoid risking a possible temporary heart failure or permanent aggravation of the heart condition. The avoidance of overexertion is very important, and the ability of a patient with organic heart disease "to carry on ordinary physical activity without discomfort" does not seem to me to be so universally applicable to school children as to adults. High school pupils, especially, routinely indulge in vigorous physical training and competitive sports which may call for extraordinary physical activities that are not safe for one with heart disease, even if the functional classification is class 1.

Furthermore, the older children, in the high schools, can be taught the danger signals, and warned to cease activity upon becoming aware of palpi-

tation or dyspnea. The younger children, however, in the elementary schools, may frequently fail to remember these sensations of heart beating and shortness of breath. Taxing the heart that has a chronic structural defect, such as valvular lesion, with a great amount of non-competitive activities may be often harmless. When heart disease is in the active stage, however, the problem is a more difficult one, and much greater precaution has to be exercised against further damaging the myocardium or causing a reactivation of a quiescent lesion. In other words, a strain on the mechanical defect of the circulation is of little danger. Inflammation, or activity of infection, however, requires not only restricted activities, but rest and prolonged convalescence for arrest or recovery of the process. Some systemic conditions as underweight, overweight, or the presence of other relevant physical defects in cardiacs may also require a suitable modification of the general principles of restriction of physical activities. When a complete cardiac diagnosis (etiological, anatomical, physiological and functional) is considered together with the full meaning of the numbered physical activities, the correlation of the functional capacity of the cardiac with the restriction of physical activities in the school becomes facilitated. Still, it is difficult to be dogmatic, as cardiacs with different anatomical diagnoses, although having the same functional classification, may require different restrictions of physical activities. I realize also, that my correlations may appear to some physical health educators to be too conservative, and to some physicians to be too radical. Experience has shown, however, that to err on the safer side is a mistake on "the side of the angels." I have therefore been recommending the following correlations:

TABLE IV
Correlation of Functional Capacity with Restriction of Physical Activities

Functional capacity	Physical activity Number allowed (highest)
(No school child with organic heart disease)	No 1
Class 1 (mild cases of congenital acyanotic or acquired lesions)	No 2
Class 1 (depending on the anatomical and physiological diagnoses)	No 3, 4 or 5
Class 2a	No 6 or 7
Class 2b	No 8 or 9
Class 3	No 9

WHEN IS RHEUMATIC INFECTION INACTIVE?

The question of whether rheumatic heart disease is in the inactive stage is particularly important to decide before the child is allowed to attend school, or return to it after any acute illness. As previously mentioned, the problem is also vital for the determination as to how much the child should be allowed to do in the school. It may be well, therefore, to review the his-

tory, physical signs and other findings that assist in ruling out activity of rheumatic infection

During the inactive stage of rheumatic infection

- 1 The child is free from any symptoms relevant to the infection
 - 2 He presents a good general appearance and absence of pallor or cyanosis
 - 3 He has good body weight
 - 4 He has a rectal temperature of 100° F or less
 - 5 His pulse rate is not over 100 a minute, and after exercise the rate returns to pre-exercise rate within three or four minutes
 - 6 He is free from fatigue when not exercising
 - 7 His systolic blood pressure and pulse pressure are within normal limits
 - 8 There is cessation of increasing cardiac enlargement
 - 9 There is freedom from evanescent adventitious pericardial, myocardial or endocardial sounds, pathologic conduction, or signs of heart failure
 - 10 There is freedom from a focus of active infection, as in the upper respiratory passages
 - 11 There is freedom from rheumatic nodules, skin eruptions, or hemorrhages
- Further investigations confirming the inactivity of the infection are
- 12 A normal hemoglobin, and red and white cell counts
 - 13 A sedimentation rate within normal limits
 - 14 A normal respiratory vital capacity
 - 15 An electrocardiogram that is free from deviations suggestive of rheumatic heart disease (Although not pathognomonic, prolongation of the P-R interval, alterations of the rhythm normal to children, and certain S-T or R-T and T-wave changes are characteristic deviations from electrocardiograms that might otherwise be considered within normal limits)
 - 16 An unchanging cardiac contour on roentgenologic and esophagaphic tests

DOES HEART DISEASE BECOME WORSE DURING SCHOOL YEARS?

Whether school life aggravates a child's heart condition depends much on several factors entering into the condition of the cardiac and his hygiene of life. It depends on an early complete cardiac diagnosis, a suitable restriction of physical activities, avoidance of school attendance during the active stage of the infection and, as previously mentioned, adequate convalescence after any other disease before school attendance is resumed. In my experience, heart disease frequently develops during—not necessarily because of—school activities, and in many cardiacs the condition becomes aggravated during the average twelve years of education. Space does not permit the citation of numerous examples. On the other hand, I have seen

many pupils who have gone through their greater part of school life with hardly any aggravation of the cardiopathy. It is true that a person with rheumatic heart defects can usually live comfortably the larger part of the span of expected life, but there are exceptions. Generally speaking, the prognosis of the child with heart disease depends on the early discovery of the condition, the degree of cardiac enlargement, the state of myocardium and the particular valves involved, the rhythm, the exercise tolerance, the education and preparation for a vocation with minimum additional damage to the heart, and the selection of a suitable vocation and harmless avocations.

CONCLUSIONS

1 The medical records of 33,293 children enrolled in Philadelphia public schools have been reviewed for abnormal heart findings. Of 863 pupils listed for observation of their hearts by 11 school physicians, 391 were considered worthy of studying. The study has been made with the aid of an adequate history of juvenile rheumatic infection, and physical examinations for the detection of circulatory diseases. Examination was made twice at an interval of about one year, and in many cases, a third examination was made in 1936. The thermometer, stethoscope, and blood pressure apparatus were used, but, with several exceptions, no other instrument of precision was employed.

2 For recording moderate cardiac hypertrophy, a new landmark on the anterior chest wall is being suggested. Its name is "preaxillary" line. The preaxillary line is an imaginary line on the front of either side of the chest, drawn vertically downward, midway between the midclavicular and anterior axillary lines, and parallel to them. It divides vertically the surface area of the chest wall between the midclavicular and anterior axillary lines exactly in half. Unlike the parasternal line which is similarly drawn from the medial half of the clavicle, the preaxillary line does not take origin from the outer half of the clavicle. The advantages of the use of the preaxillary line in chest examinations are described.

3 It is agreed that the parents, the family physician, the pediatrician, the cardiologist, and the hospital clinics form the main agencies protecting the children against the spread and aggravation of juvenile rheumatic heart disease. However, it is suggested that the school physician and nurse, and the school principal should also be enrolled in a permanent campaign to assist in the detection and amelioration of rheumatic heart disease in children. The school years are a very important period in the child's physical life and development, and have greater potentialities for the good or evil of a child with heart disease than of a healthy pupil. Perhaps the combined efforts of those named above can guide many of these unfortunate children more safely through the early educational years, prepare more wisely for a suitable vocation, and at the same time choose safe avocations. It is possible that such

wholehearted cooperation may reverse the tide, and cause a decrease in the incidence of rheumatic heart disease, not only in children, but in adults

Acknowledgments Directly and indirectly, a number of physicians, a greater number of nurses and clerical assistants, have kindly helped to assemble the data which made this report possible. Several school principals have cooperated even to the extent of arranging for physical examinations after the schools had officially closed. I regret the names are too numerous to mention here. I shall therefore be able to express my gratefulness only to Dr. Walter S. Cornell, Director, Medical Inspection of Public Schools, for his valuable advice, Drs. Samuel Baron and M. W. Benjamin, for their frequent help, and Miss Fay Ziegler and Miss Marie A. Gallagher for their diligent work in tabulating the data. Finally, may I be pardoned if I specifically mention here my great obligations to my wife in the preparation of this report.

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GONOCOCCAL ENDOCARDITIS TREATED WITH ARTIFICIAL FEVER (KETTERING HYPERTHERM) *

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It has been known for many years that the gonococcus is quite susceptible to heat ^{1,2} It remained for Carpenter, Boak, Mucci and Warren ³ to determine by careful thermal death time gradient studies that 99 per cent of the cultures of several strains of gonococci are killed in vitro by 4 to 5 hours exposure to a temperature of 105.8° F With the Kettering hypertherm even higher temperatures over longer periods of time may be administered to patients with comparative safety The excellent clinical results obtained with this form of treatment in various gonococcal infections strongly suggest that the thermal death point of the organisms in vivo approximates that found to exist in the in vitro experiments of Carpenter et al

Within the last 15 years numerous authors have reported case studies of gonococcal endocarditis ^{4,5,6} A uniform feature of the reports has been the expression of a gloomy attitude regarding the efficacy of any form of treatment, once the organism has become established on a heart valve The present communication is concerned with the results obtained by treating one case of verified and one of probable gonococcal endocarditis with artificial fever (Kettering hypertherm) † The former is reported in detail as there have been no reports of necropsy findings in patients with gonococcal endocarditis who died after fever treatment

CASE I

History L L, a colored man of 24, was admitted to the Vanderbilt University Hospital July 15, 1936, complaining of weakness and chills Five weeks previously he developed coryza, sore throat, non-productive cough, slight pain in the upper mid-portion of the chest, generalized aching, malaise and fever A few days later a chill occurred, followed by slight swelling of the ankles, left knee and right elbow These joints remained painless and the swelling lasted only a few days After 10 days confinement to his home he felt much better although he did not entirely recover On July 10 he noticed a sudden increase in weakness and malaise He became dyspneic on exertion and developed edema of the feet and legs The next day he had a chill lasting 30 minutes On July 15 he had a second chill and his temperature was 105° F

There was no history of gonorrhea or syphilis

Physical Examination He was a well developed and well nourished negro who appeared acutely ill He perspired freely and the respirations were fast and deep The sensorium was clear The mucous membranes and conjunctivae were pale and

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† This apparatus was supplied to Vanderbilt University Hospital through the kindness of Mr C F Kettering, director of the Division of Research, General Motors Corporation, and Dr Walter M Simpson, Miami Valley Hospital, Dayton, Ohio

slightly icteric. The skin was hot (temperature 104.4°) and exhibited numerous small red lesions over the tibiae. These were 1 to 3 mm in diameter and did not blanch on pressure. The nasal mucosa was injected and swollen. The tonsils were moderately large and reddened. The lungs were normal on physical examination. No cardiac enlargement was noted, but there was a long, loud, harsh systolic murmur of maximum intensity at the apex and transmitted to the left axilla and over the entire precordium. The second pulmonic sound was accentuated. The pulse was rapid (100), regular and of good volume. The blood pressure was 118 mm of mercury systolic and 80 diastolic. The abdomen was distended and signs of a small amount of free fluid were present. The liver edge was firm and smooth and extended 4 cm below the right costal margin. It was not tender. The spleen could be felt 5 cm below the left costal margin. A circumscribed smooth scar was present on the prepuce. The prostate was normal in size but slightly soft. The joints were normal. There was moderate pitting edema of the feet and legs.

Laboratory Data Urine, clear and yellow, specific gravity 1.008, acid reaction, no albumin and no sugar, the sediment contained occasional white blood cells but no red blood cells or casts. Red blood cell count 3,550,000, hemoglobin 8.5 gm, white blood cell count 15,100, neutrophils 61 per cent, eosinophils 1 per cent, lymphocytes 33 per cent, monocytes 5 per cent, no malarial parasites. The Wassermann reaction and the Kahn test were positive. Non-protein nitrogen 21.4 mg per cent, icterus index 9, total serum protein 7.07 gm per cent (albumin 2.62, globulin 4.45). Stools were of normal appearance and showed no pus, blood or parasites. Bromsulphalein liver function test 40 per cent retention in 30 minutes. The Takata-Ara test was positive. The galactose tolerance test showed a decrease in tolerance. The red blood cells exhibited normal resistance to hypotonic salt solutions. Roentgen-ray examination of the chest, pelvis and abdomen was essentially normal. Agglutination tests with *B. typhosus*, *B. paratyphosus* A, B, *B. melitensis* and *B. abortus* were all negative.

Course He ran a septic course with constant leukocytosis (averaging 12,000), intermittent fever with daily fluctuations of 6 to 10 degrees and occasional chills. Jaundice and ascites slowly but steadily increased. Frequent examinations of "thick drop" preparations for malarial parasites were negative. He was given a therapeutic test with quinine for five days, without notable change. During the three weeks preceding death (August 14) he received weekly injections of bismuth salicylate and was given 25 drops of a saturated solution of potassium iodide three times daily. Blood cultures obtained July 16, 17, and 20 showed no growth, while those obtained July 22 and 29 and August 6 contained gonococci. On August 6, the urine showed a small amount of albumin, bile, a few erythrocytes and leukocytes and numerous granular and cellular casts. Evidence of renal damage rapidly increased. By August 8, the 24 hour urine excretion had fallen from 2,000 to 400 cc, in spite of a fluid intake of over 2,500 cc, and the urine contained a moderate amount of albumin, bile, and numerous red blood cells. On August 8, 3,500 cc of turbid reddish yellow fluid were withdrawn from the peritoneal cavity, its specific gravity was 1.004, the erythrocyte count 5,625, leukocyte count 1,875. No bacteria were demonstrated by smear, culture or guinea pig inoculation.

With full recognition of the extremely gloomy prognosis because of the presence of gonococcal endocarditis associated with severe liver and renal damage, he was placed in the Kettering hypertherm on August 10. His temperature was maintained at an average level of 105.5° F (rectal) for six hours. To our surprise he bore this treatment fairly well. He was afebrile for the next 20 hours and his temperature never returned to as high a level as had previously existed. However, he appeared more stuporous. His 24 hour excretion of urine was 700 cc. On August 11 a blood culture was made from which no gonococci were grown. On August 12 he became anuric. On August 13 he received his second fever treatment. On this occasion his

temperature was held between 106 and 107°, averaging 106.7°, for five hours. This treatment as the first, was apparently well tolerated. However, the stupor increased and he remained anuric (non-protein nitrogen 133 mg per cent, carbon dioxide combining power 29.1 volumes per cent). He died on August 14.

Clinical Impression Acute bacterial endocarditis (mitral valve), due to gonococcus, syphilitic cirrhosis of liver, ascites, jaundice, embolic glomerular nephritis, uremia, anemia secondary to infection.

Necropsy Report Autopsy performed two hours post mortem. The sclerae, subcutaneous fat and, in varying degrees, the viscera were jaundiced. Peritoneal cavity contained about 1,000 cc of greenish-red fluid. Pericardial cavity. The surfaces were smooth and glistening, about 40 cc of clear fluid were present. Heart Weight 270 grams, epicardium, myocardium and all valves, except the mitral, appeared normal. On one mitral leaflet was a firm non-friable vegetation 6 to 9 millimeters above the surface. On the opposite leaflet was a similar but smaller vegetation. These vegetations were so firmly adherent that it was felt certain that they contained a great deal of fibrous tissue (figure 1). There was slight ulceration of the margin of one cusp. The chordae tendineae appeared normal. Lungs. A small amount of atelectasis was present in the lower lobes. Gastrointestinal tract Negative. Liver Weight 1,800 grams. The surface was nodular and in several places broad fibrous bands cut deep in the parenchyma (figure 2). A flattened, tongue-like projection extended over the spleen. Much resistance was encountered in slicing the liver. Cut sections revealed extensive scarring with broad fibrous bundles interlacing and surrounding islands of raised, reddish-yellow tissue. Scattered here and there, but denser in the left lobe than elsewhere, were varying sized and shaped grayish yellow, soft areas of necrosis with surrounding red zones. The gall-bladder and bile ducts appeared normal. Spleen Weight 940 grams, the pulp was firm, dark red, friable and densely studded with infarcts of varying ages, some of the older ones having become somewhat softened. Kidneys. The weight of the right kidney was 210 grams, and the weight of the left kidney was 200 grams. The capsules stripped easily, leaving smooth surfaces. The cut surfaces were pale and showed many small reddish splotches, thought to represent small hemorrhagic foci with some necrosis. Genito-urinary tract. The ureters, bladder, seminal vesicles, epididymes and prostate were normal. Brain Negative.

Microscopic Examination Heart. Nothing remarkable was found except in the mitral leaflets. At the site of the vegetations were seen dense hyalinized fibrin deposits containing scattered polymorphonuclear leukocytes. There were two small foci of polymorphonuclear leukocytes beneath the surface of the valve. Beneath this process was a more chronic inflammatory reaction with an associated healing reaction as evidenced by the invasion with many fibroblasts and the formation of many small blood vessels (figure 3). Lungs. Atelectasis and slight passive congestion were present. Liver. The normal architecture of the liver was almost entirely destroyed. The sections showed a very large amount of fibrous tissue encircling varying sized islands of liver cells. In the fibrous tissue were many bile ducts, scattered lymphocytes, plasma cells and macrophages. In some areas there were polymorphonuclear leukocytes in and around the ducts. All the liver cells in some of the lobules were normal, whereas others had normal cells in the periphery, but the entire midzonal and central part showed uniform karyolysis of both nucleus and cytoplasm. At the edge of these areas of necrosis were rows of polymorphonuclear leukocytes. No thrombi were seen in vessels. No typical gummata were present. Spleen. There was marked engorgement of all sinuses and hemorrhages were scattered throughout the organ. Many polymorphonuclear leukocytes were present in the pulp. There were many areas of necrosis partly infiltrated with blood which had the appearance of infarcts. There was a proliferation of fibroblasts in some of these areas. Pancreas. One acinus



FIG 1 Healing gonococcal vegetations on mitral valve. Arrow 1 indicates a small ulcerated vegetation undergoing healing. Arrow 2 indicates the site of a lesion in which the healing process is more advanced.



FIG 2 Liver Note the typical cirrhotic changes on the surface of the organ and the huge scars with resulting deformity (hepar lobatum)

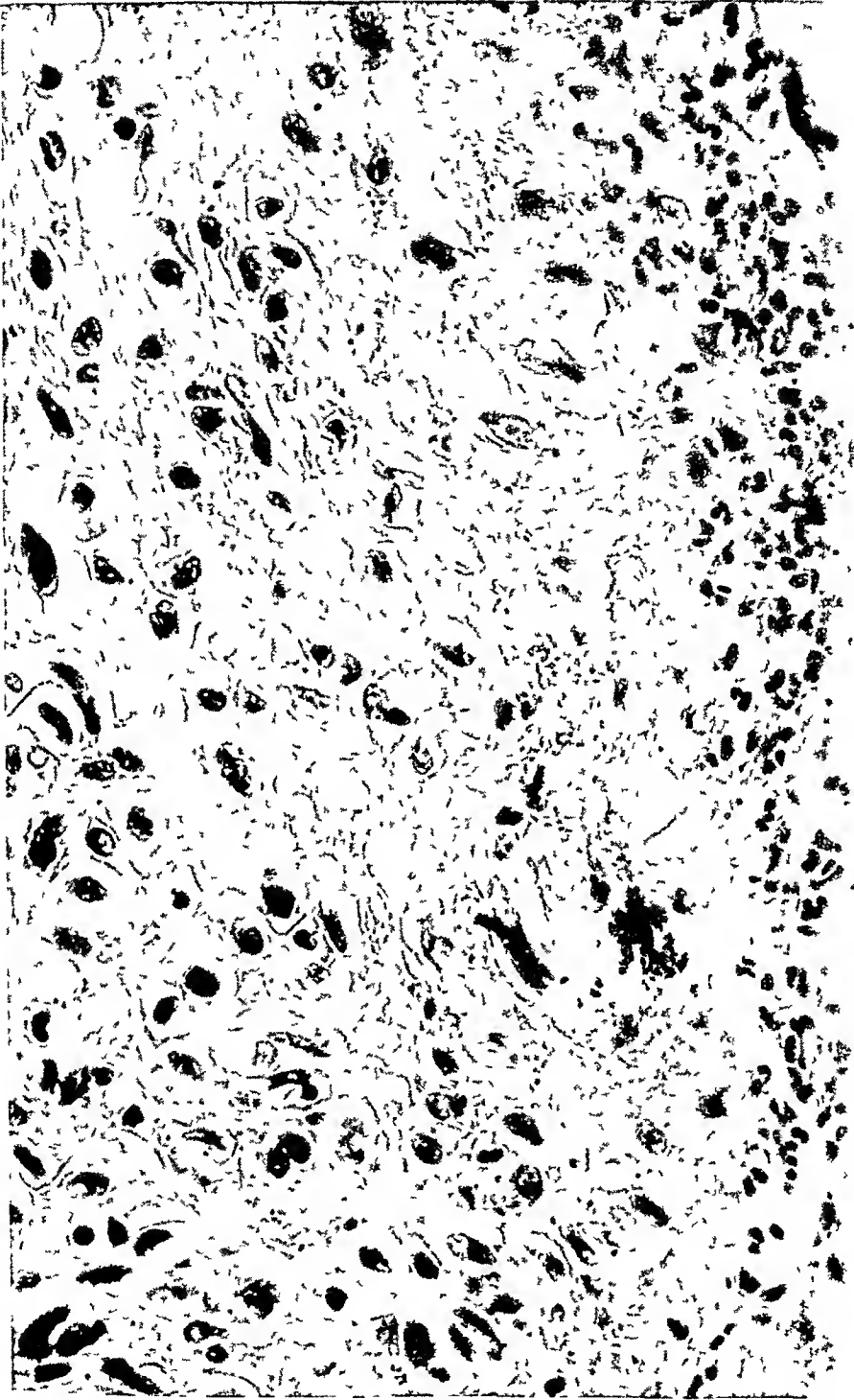


FIG 3 H and E stain Healing on mitral valve ($\times 500$) (See figure 1)

showed polymorphonuclear cells in its lumen whereas the remainder appeared normal, but there was edema and slight lymphocytic infiltration in the interstitial tissue. Adrenals: There was congestion of the vessels surrounded by foci of mononuclear cells but otherwise the organs were normal. Kidneys: There was swelling of the glomerular endothelium and a few of the endothelial cells were pyknotic. Many of the glomeruli showed intra-capillary hyalinization. The capillaries contained an increase in polymorphonuclear leukocytes. Some of the tubules contained polymorphonuclear leukocytes and albuminous material. The interstitial tissue was infiltrated with macrophages, plasma cells and lymphocytes. Seminal vesicles, epididymis, testis, bone marrow and brain: Essentially negative. *Bacteriology*: Smears and cultures from the vegetations yielded no organisms. Cultures of the heart's blood gave no growth. Smears from the prostate, liver and spleen contained no organisms. Stains of the mitral vegetations with hematoxylin-eosin, Gram's iodine and Giemsa stain failed to reveal organisms.

Anatomical Diagnosis: Acute endocarditis, mitral, gonococcal, syphilitic cirrhosis of the liver, infarcts in spleen, embolic, acute nephritis, embolic, pulmonary atelectasis, obstructive (with mucus), passive congestion of lungs, icterus, ascites.

This case report is of especial interest because of the following points: (1) an extremely ill person was treated in the Kettering hyperthermia without treatment complications, and (2) following treatment with hyperthermia gonococcemia disappeared ante mortem and the heart's blood and gonococcal vegetations were found sterile post mortem.

The clinical diagnosis was difficult because of the co-existing liver disease. By the time the data were correctly analyzed the patient had experienced a progressive septic illness for five weeks and exhibited evidence of severe liver disease and renal damage with uremia. His condition was such (uremia, hepatic insufficiency) that it was felt that he might not survive the first fever treatment. However, it was well tolerated. A blood culture taken the following day was sterile. The second treatment resulted in no reaction which could be related to hyperthermia in spite of the fact that the uremic state steadily progressed. At necropsy no organisms could be grown from the mitral vegetations or heart blood and none could be found on smear or with special tissue stains. There was but a small amount of fibrin and only a few polymorphonuclear leukocytes at the site of the vegetations and evidence of healing was well established.

The areas of necrosis in the liver were interpreted as resulting from emboli or from an exacerbation of syphilitic endarteritis brought about by the combination of bismuth, iodides and heat. The possibility that fever treatment may have intensified the manifestation of uremic intoxication was considered. The necropsy findings threw no light upon this.

CASE II

History: On May 2, 1936 there was admitted a white male salesman, aged 46, who for three weeks had been having "cramps" in various muscles, had felt easily fatigued, and had noted loss of energy. Most of his symptoms, however, appeared very suddenly four days preceding admission when he developed a "hard chill," a fever of 104° F, generalized aching and profound malaise. The following morning

he noticed numerous small, sore, red spots scattered in the skin of various parts of his body, but localized chiefly on the extremities. The day preceding admission he developed pain and slight swelling in the knees, ankles and wrists.

He had gonorrhea at the age of 26.

He was told eight years before the present illness that he had a "slightly leaking heart valve."

Physical Examination On admission he appeared acutely ill. His skin was hot (temperature 103° F) and he was perspiring freely. Scattered on the distal portions of the extremities, and to a much less extent over the other parts of his body, were numerous circumscribed, purplish-red areas in the skin, varying in diameter from 2 mm to 1 cm. Some of these were slightly tender. Many showed a central white area of necrosis and a few showed vesiculation with accumulations of seropurulent fluid. No petechiae were present in the mucous membranes. The blood pressure was 145 mm of mercury systolic and 90 diastolic. The apex beat was in the fifth inter-space, 9 cm from the midsternal line. There were no shocks or thrills over the precordium. There was a moderately loud, blowing, systolic murmur, best heard at the mitral area, transmitted to the left axilla. There was slight swelling and pain about the ankles and wrists. Only slight pain was excited by manipulation of the joints and it was felt that the inflammation was in the periarticular tissues rather than in the joints proper.

Course His course was that of septic illness with "spiking" temperature chart and occasional chills. The leukocytes ranged from 8,000 to 12,000 per cm. The petechiae gradually faded over a period of four weeks. The swelling about all the joints, except the right ankle, subsided in a few days. During the second week the right ankle became tremendously swollen, exquisitely tender and red. Pus was aspirated from this joint and gonococci were demonstrated by smear and culture. During the second week in the hospital the systolic murmur at the mitral area changed in quality and intensity. It became louder and harsher. No gonococci could be demonstrated from urethral or prostatic excretion, but there were many pus cells. Blood cultures taken on May 2, 4, 8 and 15 yielded no growth. May 4, agglutination tests with *B. typhosus*, *B. paratyphoid A*, *B. paratyphoid B*, *B. melitensis*, *B. abortus* and *B. proteus X-19* were negative. These agglutinations were repeated May 14 and were again negative. An electrocardiogram, May 4, showed the S-T segment to form the ascending limb of a high peaked, diphasic T-wave in Lead II, S-T segment was of low origin in Lead III. On May 8 the complexes were normal except that T₁ and T₂ were slightly diphasic. On May 19, the complexes were interpreted as being due probably to transient myocardial disease (embolism?).

He was placed in a Kettering hypertherm on May 26. His temperature was maintained between 105 and 106° F for five hours. Following this treatment his temperature returned to normal and remained practically normal thereafter. There was a marked decrease in the inflammatory reaction about the ankle. It was noted that the mitral murmur was less harsh. On May 29 he was given a second treatment. His temperature was held at between 106 and 107° F for five hours. The ankle continued to show steady improvement. He was given a third treatment June 2, when, after it had been maintained at 106.5° for two hours, his temperature suddenly rose to 108.2°. The patient developed evidence of impending collapse and treatment was discontinued. June 10 he was discharged free of symptoms, except for slight discomfort in the right ankle.

Six months later the patient reported that he had returned to his work a few weeks after discharge from the hospital. His "follow-up" examination at this time was essentially normal except for the persistence of a faint systolic murmur at the mitral area.

The sudden onset of this patient's illness with a chill and high fever, the presence of numerous large petechiae with areas of central necrosis, the high, septic temperature with occasional chills, the transient multiple arthritis with subsequent development of acute purulent monoarticular arthritis from which gonococci were obtained, the presence of transient electrocardiographic alterations indicating acute changes in the myocardium, and the change in character of the apical murmur constitute convincing evidence of severe (metastatic) gonococcal infection and strongly suggest that gonococcal endocarditis was present. Recovery was prompt and complete, following treatment with artificial fever.

SUMMARY

1 A case history of proved and one of probable gonococcal endocarditis treated in the Ketting hypertherm are recorded.

2 In the proved case, fever treatment resulted in sterilization of the blood and, as established at necropsy, sterilization and healing of the endocardial vegetations. Death was due to co-existing syphilitic cirrhosis of the liver and uremia. At autopsy no pathologic changes were noted in the viscera which could be attributed to the effect of fever treatment per se.

3 In the case designated as probable gonococcal endocarditis with co-existing acute gonococcal arthritis, fever treatment resulted in prompt recovery.

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SEVERE BONE-MARROW DEPRESSION FOLLOWING ARSPHENAMINE, REPORT OF TWO CASES WITH RECOVERY

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THE authors delayed reporting the following two cases of arspenamine bone-marrow depression for several years in order to make certain of the permanency of the recovery which occurred in both cases. The blood dyscrasias occasionally caused by arspenamine have been reported in the literature mainly under the headings of their outstanding clinical manifestations, such as granulocytopenia, agranulocytosis, thrombocytopenia, or aplastic anemia. A study of these reports and of the two patients who were followed carefully on the wards of Beth Israel Hospital has confirmed our belief that most cases may best be considered as early or late instances of the same toxic process which in its severest form causes complete aplasia of the bone-marrow.

CASE REPORTS

Case 1 L W, male, aged 50, cloak manufacturer, admitted May 4, 1933 because of weakness, fever, joint pains and frontal headaches of two weeks' duration, and a rash over his lower extremities which had appeared the preceding day.

The patient had a chancre confirmed by dark-field examination in 1918. Anti-luetic therapy was begun immediately and continued for two full years. The Wassermann examination was positive only once. After this there were no complaints referable to the disease except for a feeling of numbness and cold in the toes and finger tips for three years before his present illness. Two months before admission (March 1933) following exposure to infection the patient again developed a chancre, also confirmed by dark-field examination, thus providing an excellent example of that rarity—a second chancre. Intravenous therapy was begun and nine injections of salvarsan were given, twice weekly. The last six injections were followed in four to five hours by marked general reactions with chills and fever. The patient felt worse after each reaction, finally taking to bed two weeks before admission because of weakness, lassitude, aching joints, severe frontal headache, and moderate fever. The case was diagnosed as grippe, but the pyrexia and other symptoms failed to disappear. Three days before admission to the hospital, while crossing his left knee over his right, he experienced a sudden click in his left calf, this area became painful and hard, but not reddened. On the day of admission he developed a rash on both lower extremities which did not itch.

Physical Examination The patient appeared chronically ill, markedly pallid. No lymphadenopathy was present. The pupils were equal, regular and reacted well to light and accommodation. The tongue was not atrophic, the gums were normal, the teeth false. The heart was not enlarged, a soft systolic murmur was heard at the apex. The lungs were emphysematous. The liver was palpable two fingers below the costal margin as a smooth, non-tender mass, the spleen was barely palpable. Knee jerks, ankle jerks and other reflexes were normal. There was no loss of vibration or

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position sense There were fine petechial hemorrhages (purpuric) over both legs, both arms and in the right axilla The tourniquet test (Rumple-Leeds phenomenon) was positive The left calf muscle was hard and tender

Laboratory Data

Urine	June 5	Sp gr 1.018, acid, amber, very faint trace of albumin, no glucose, no casts, no red blood cells, occasional white blood cells
	June 8	Arsenic is present
Feces	June 6	Blood and bile present
Venous pressure	June 5	7.5 cm
Sedimentation rate	June 5	130 mm in 45 minutes
	July 16	90 mm in 45 minutes
Icteric index	June 29	7
Wassermann	June 5	Negative
	June 18	Negative
Blood culture	June 29	Sterile
Blood chemistry	June 5	Glucose 133 mg per cent, non-protein nitrogen 26 mg per cent
	July 19	Fibrinogen 2.1 g/100 c.c. plasma
Culture of pus from thigh	July 18	<i>Staphylococcus aureus</i>
Roentgen-ray of chest	June 8	Shows normal heart, aorta and lungs
Electrocardiogram	June 9	Sinus tachycardia

The blood counts and the dates of transfusions are shown in the following table

Progress Notes The patient entered with a temperature of 101.2° F, but this rose to 106.2° the next evening, and varied between 102° and 105° for the next week. Intravenous sodium thiosulphate and repeated intramuscular injections of adenine and pentnucleotides in the first two weeks of his stay did not prevent the continued fall of the white blood count from 1900, with 48 per cent polynuclear cells, to 1,350 with 20 per cent polynuclears on the seventh day (June 10) and 1,600 with 32 per cent polynuclears on June 22, when the treatment was stopped.

A bone-marrow puncture over the upper third of the sternum was performed on the third day of his stay (June 6). The marrow was red, but appeared somewhat less cellular than normal. Microscopic examination revealed numerous normoblasts, no megaloblasts, no myeloblasts, many myelocytes, *metamyelocytes* and *stuffs*, the latter two predominating. There were few mature segmented neutrophils. No megakaryocytes were seen. The fact that pathologically the bone-marrow showed no increase in younger cells but an apparent decrease in mature elements ruled out definitely a truly organic aplastic anemia. The most probable diagnosis, considering the normal cellular elements found on biopsy and the neutropenia, thrombocytopenia and anemia shown by the peripheral blood was a toxic inhibition of the bone-marrow due to the arsphenamine. These bone-marrow findings were the rationale for transfusions, which were repeated about twice weekly in spite of failure of the patient's blood to respond to them.

June 17, 1933 The patient showed dryness and desquamation of the skin of the upper extremities, chest and back. The dermatologist considered the skin eruption an arsenical exfoliative dermatitis. There were many new petechiae over the chest, back and mouth at this time.

June 22 There was a small area of beginning ulceration between the hard and soft palate which lasted only a few days.

June 27 Purpuric manifestations were increasing while the white blood count showed a steady rise in polymorphonuclears. For the first time the patient showed

TABLE I
Blood Counts and Transfusions (Case 1)

Date	Erythro- cytes	Hgb %	W B C	Total		Staff	Seg	Eos	Mono- nuclears		Plate- lets	Other Findings	Trans- fusions
				Poly- nuclear	Mono- nuclear				Lympho- cytes	Mono- cytes			
6/4	2,290,000	55	1900	48	52	2	46			6	Dimin 50,000	1 normoblast	
6/5	2,000,000	48	2000	23	77	8	14	1	71	6		slight macrocytosis, toxic degen of polys, 1 myelocyte	
6/7	2,360,000	48	1800	11	89	1	8		89	0			300 c c
6/9	2,390,000	47	1600	16	84	6	8	2	80	4		slight toxic degen of polys, no poiki- locytes, no poly- chrom	500 c c
6/10	2,890,000	56	1350	20	80	7	12		72	8	43,350	aniso, polychrom	
6/12	2,960,000	55	1700	18	82	6	12		80	2		aniso, polychrom	400 c c
6/14	2,660,000	52	2000	20	80	4	16		77	3		aniso, polychrom	
6/15													500 c c
6/17	2,820,000	56	2050	26	74	9	13	1	62	12	30,900	2 plasma cells, 2 my- elocytes	
6/19													500 c c
6/22	2,480,000	55	1600	32	68	6	22	3	66	2		1 myelocyte, poly- chrom	300 c c
6/26	2,600,000	59	1900	39	61	6	20	1	54	7		2 myelocytes	
6/27	3,220,000	61	2500	32	68	9	21		63	5		1 myelocyte	300 c c
6/29	2,680,000	60	2000	29	71	7	22	1	60	10		marked degen of neutrophils	
6/30											35,000		300 c c
7/1	2,620,000	51	2400	24	76	4	17		64	12		2 myelocytes	
7/3													300 c c
7/5	2,590,000	52	3400	27	73	5	19	2	59	13		1 myelocyte	
7/7													300 c c
7/8	2,630,000	55	2500	39	61								
7/10													300 c c
7/12	2,700,000	52	4400	50	50	10	40		37	13		marked aniso	
7/13	2,670,000	50	5150	42	58	9	33		48	10			
7/14			4300	34	66	9	24		51	15		1 myelocyte	
7/15	2,460,000	45	4300	39	61	7	30	2	54	7			
7/17	2,220,000	46	3200	37	63	8	28	1	52	11		marked aniso, poly- chrom	300 c c
7/18											8,880		
7/19	2,520,000	50	3600	44	56	7	36	1	42	14			
7/21	2,540,000	48	4400	44	56	4	40		50	6			300 c c
7/24	2,810,000	52	4000	48	52	2	46		47	5			
7/26	3,050,000	54	5000	43	57	4	36	1	52	5			
7/28	3,180,000	58	4000	47	53	4	42	1	45	8			
7/31	3,260,000	59	4600	27	73	2	24	1	69	4			
8/1			4500	36	64	3	30	2	60	4			
8/2			4050	28	72	2	23	3	68	4			
8/3	2,950,000	56	3800	34	66	4	27	4	59	7			300 c c
8/4	3,370,000	62	4400	44	56	7	32	4	53	3			
8/7	3,430,000	64	4100	36	64	4	31	1	60	4			
8/9	3,230,000	62	4400	35	65	2	31	2	60	5	9,900		
8/14	3,240,000	62	4550	30	70	2	27	1	65	5			
8/16	3,130,000	60	3600	38	63	1	34	2	57	5		slight macro- and microcytosis	

some clinical improvement. The temperature, which ranged between 101° and 106° F rectally the first three weeks, sought a lower level (100° to 103° F) now.

June 29. An erythematous area on the right hip was noticed, with a tendency to pustule formation, this cellulitis became softer and disappeared in about two weeks.

July 11. The hematoma of the left calf muscle, which always had been hard and non-tender, became softer and more tender.

From July 12 on, the blood and clinical picture showed steady improvement (table 1). There was only a sub-febrile temperature at this time, which later became normal. The patient felt a daily increase in strength. Upon his discharge ten and one-half weeks after admission he felt perfectly well except for the painful diffuse swelling of his left calf muscle due to an organized hematoma. His blood count on this day (August 16) was: Rcd blood cells 3,130,000, hemoglobin 60 per cent, white blood cells 3,600, polymorphonuclears 48 per cent. Discharge Diagnosis: Arsplenamine panmyelophthisis. Arsenical exfoliative dermatitis. Organized hematoma of left calf.

Follow-Up Notes. Patient had no complaints at any time when a follow-up blood count was done. The general condition was good, the heart, lungs, skin and joints negative. Blood counts were as follows:

Date	R B C	Hgb %	W B C	Polys	Monos	Staff	Eos	Lymphs	Monos
2/ 8/34	4,070,000	69	5,800	46%	54%	3%	3%	50%	4%
9/23/35	3,780,000	86	5,700	53%	47%	1%	4%	42%	5%
1/ 7/36	4,530,000	90	7,100	47%	53%	2%	5%	43%	10%

Comment on Case. The importance of the bone-marrow puncture in this case cannot be overemphasized, for it indicated that, although findings in the peripheral blood were those of an aplastic anemia (granulocytopenia, thrombocytopenia and erythrocytopenia) the bone-marrow was not aplastic. Its function was simply suspended. The biopsy bolstered up our faith in the efficacy of persistent transfusions during the first four weeks when the patient failed to show any clinical improvement, and when his condition appeared hopeless, because of the marked asthemia, hyperpyrexia and bleeding. We believe the repeated transfusions saved this man's life by tiding him over the acute emergency of toxic inhibition of the bone-marrow. It is interesting to note that when the patient's condition began to improve and his blood to show a rise in the polymorphonuclears, the infected areas on the right buttock and left calf became soft, fluctuant and purulent, and showed the more typical picture of an acute infection which is undergoing healing, whereas previously these areas were more indolent and showed no pus. This contrasts with the case of dysplastic granulocytopenia reported by Weiss and Goldbloom¹ where clinical improvement in an anal slough did not occur even though leukocytosis (up to 40,000 cells) followed several weeks of granulocytopenia. That patient died in spite of the return of the neutrophils because these cells, although plentiful in number, were of deficient quality, due to an irreparable injury to the mother-cell. In our present case, however, there was apparently no such injury to the mother-cell, for once

the bone-marrow resumed its hematopoietic function the patient's condition improved rapidly, and was no longer serious. The follow-up blood counts show that the recovery was complete, and there was no tendency to relapse.

Case 2 E. L., male, aged 32, manager, admitted June 19, 1933 with progressive weakness and bleeding from nose and gums for about one month.

The patient discovered he had a four-plus Wassermann in the course of a routine study for a "cyst" near the rectum about six months before. He immediately underwent a course of arsphenamine therapy, receiving an injection once a week for six weeks, until his Wassermann was negative. There were no immediate ill-effects except for mild nausea on the injection days. After this he received seven more injections at three-week intervals. The dosage was rather high (from 0.5 to 0.9 grams). He noticed that he was becoming progressively weaker and that he tired very easily. About three to four weeks before admission he began to bleed from the gums, and later had bleeding from the nose one night. The bleeding from the gums was intermittent, and became much worse five days before admission. Three days before his entry into the hospital his vision, which was failing, became so poor that he could not read the newspaper headlines.

Physical Examination The patient appeared extremely pale, subicteric, chronically ill. Pupils normal. Fundi rather pale with numerous hemorrhages, mostly along the course of vessels. The tongue was coated, the breath fetid, the gums bleeding. Slight enlargement of the cervical glands was present. The heart and lungs were negative. The liver was palpable at the costal margin, the spleen was not felt. The knee and ankle jerks were obtained on reinforcement. There was no loss of vibration or position sense in the lower extremities.

Laboratory Data

<i>Average Urine Analysis</i>	Sp. gr. 1.014, acid, amber, very faint trace of albumin, no glucose, no casts, rare red blood cells, rare white blood cells
<i>Feces</i>	June 20 Arsenic not present
	June 24 Blood and bile present
	June 27 Blood and bile present
	July 20 Blood present
	Aug. 23 Blood absent
<i>Venous pressure</i>	June 19 6 cm.
<i>Sedimentation rate</i>	June 19 134 mm. in 45 minutes
<i>Icteric index</i>	June 21 7
<i>Tomquist test</i>	June 25 Negative
	July 9 Positive
<i>Clot retraction</i>	June 27 Normal
<i>Bleeding time</i>	June 27 Before transfusion) 90 minutes
	June 29 (After transfusion) 3 minutes
<i>Coagulation time</i>	June 29 3.5 minutes
	Aug. 24 3 minutes
<i>Wassermann</i>	June 19 Negative
<i>Blood chemistry</i>	June 20 Glucose 133 mg. per cent, non-protein nitrogen 35 mg. per cent
	July 7 Calcium 9.8 mg. per cent, phosphorus 3.0 mg. per cent
	July 19 Fibrinogen 0.9 g./100 c.c. plasma
<i>Electrocardiogram</i>	June 20 Sinus tachycardia
	Aug. 4 Frequent ventricular extrasystoles

The blood counts and the dates of transfusions are shown in the following table

Progress Notes The patient at first was given sodium thiosulphate intravenously for two days and pentnucleotides intramuscularly for five days. This apparently had no effect on the white blood count, which fell to 1150 with 11 per cent polys on June 24 (table 2), when there was bleeding from the gums which lasted all day. In spite of repeated transfusions the patient's condition remained grave, gingival bleeding persisted, even though it would stop for a period shortly after a transfusion. Transfusions were given bi-weekly, but with little apparent effect on the blood picture. On July 25 the patient's temperature, which had remained about normal after the first week, rose to 104° F. A fissure-in-ano with large hemorrhoids and an ischio-rectal abscess were found to be the cause of the fever. The abscess was incised on July 31, after which time the temperature fell to normal. The wound failed to granulate, however, and by August 11 there was still no evidence of healing. The patient was failing fast. Bleeding from the gums and nose increased, diminishing only slightly for a short period after a transfusion. Surprisingly enough, however, about August 17 and 18 a sudden turn for the better occurred. The wound began to granulate. On August 21 the patient for the first time stated that he felt well. Though there was

TABLE II
Blood Counts and Transfusions (Case 2)

Date	Erythrocytes	Hgb %	W B C	Total		Staff	Seg	Eos	Mono-nuclears		Platelets	Other Findings	Transfusions
				Poly-nuclear	Mono-nuclear				Lymphocytes	Mono-cytes			
6/20	1,050,000	23	2300	9	91	5	4		85	6	78,759	reticulocyte 0.2%	500 cc
6/23	1,160,000	25	1600	14	86	4	10		80	6	30,900	1 normoblast	
6/24	1,230,000	21	1150	11	89	5	6		85	4			500 cc
6/26													
6/27	1,270,000	26	2000	12	88	3	8		86	2	10,900	1 myelocyte	500 cc
6/28													
6/29	1,790,000	34	1500	18	82	2	16		82		15,300		400 cc
6/30													300 cc
7/3	1,800,000	35	1600	26	75	6	18		67	8	16,900	1 normoblast, 1 plasma cell, 1 myelocyte	
7/5	2,190,000	45	1500	24	76	6	18		67	9	13,050		300 cc
7/7													300 cc
7/8	2,690,000	47	1150	25	75	9	16		63	12		2 plasma cells	
7/9	2,250,000	40											
7/10	1,860,000	38	1960	14	86	3	11		74	11		1 myelocyte, 2 plasma cells, 1 plasma cell	300 cc
7/12	2,580,000	42	2650	26	74	5	20	1	69	5			
7/13	2,460,000	39	3100	18	84	3	15		80	2			
7/14													300 cc
7/15	2,490,000	47	3000	20	80	3	17		73	7			
7/17	2,325,000	48	2700	15	85	4	10	1	69			1 myelocyte	300 cc
7/19	2,350,000	46	2050	20	80	7	13		70				
7/21	2,610,000	48	3200	20	80								300 cc
7/24	2,750,000	49	2800	18	82	4	14		77	5			300 cc
7/26	2,500,000	47	2600	17	83	6	9	1	72	11	7,500	1 normoblast	
7/28	2,250,000	41	2000	9	91	5	4		83	8			300 cc
7/31	2,200,000	40	2500	11	89	5	6		80	9			500 cc
8/1			3000	53	47	12	41		44	3			
8/2			3200	52	48	16	35	1	46	2			

TABLE II—Continued

Date	Erythrocytes	Hgb %	W B C	Total		Staff	Seg	Eos	Mono-nuclears		Platelets	Other Findings	Transfusions
				Poly-nuclear	Mono-nuclear				Lymphocytes	Mono-cytes			
8/3	1,810,000	34	2900	60	40	18	42		37	3	8,550		300 c c
8/7	1,690,000	34	3250	28	72	8	19		72				
8/8													300 c c
8/9	2,010,000	38	3500	33	67	5	28		65	3			
8/10	2,150,000	38	3450	38	62	4	34		59	2			300 c c
8/11	2,350,000	40	3650	36	64	7	28		63	1			
8/14	2,230,000	42	3600	40	60	4	34		60				
8/16	2,350,000	44	3450	33	67	5	28		63	7			
8/18	2,400,000	48	3200	41	59	2	37	2	54	5		aniso, polychrom	
8/20	2,080,000	42	4050	33	67	4	29		59	8	9,200	aniso, polychrom	
8/23	2,020,000	41	3600	41	59	4	35		52	7		aniso, polychrom	
8/25	1,890,000	38	3000	39	61	3	35	1	55	6		aniso, polychrom	
8/26													300 c c
8/27	2,210,000	44	4400	39	61	5	32	2	58	3			
8/28	1,940,000	36	3300	43	57	4	37	1	52	5		aniso, polychrom	
8/30	1,870,000	32	3800	47	53	5	51		46	7		macro- and micro-cytosis	350 c c
9/1	1,860,000	39	3600	38	62	4	34		54	8		macro- and micro-cytosis	350 c c
9/2	2,010,000	37	3800	48	52	5	42		46	6		reticulocytes 0 2%	
9/5	1,890,000	38	4000	40	60	4	35	1	34	6	7,400		
9/7	1,900,000	38	4100	46	54	4	41	1	49	5		reticulocytes 1 6%	300 c c
9/8	2,590,000	44	3600	49	51	3	43	2	48	3		2 normoblasts, macrocytosis	
9/11	2,221,000	40	3400	49	51	2	45	2	46	5	6,400	reticulocytes 0 7%	
9/14	2,340,000	42	3500	38	62	6	32		55	7		1 normoblast	
9/16	1,930,000	42	3900	47	53	5	40	2	42	11		anisocytosis	

Follow-up

1934													
1/20	4,010,000	80	6500	62	38	5	56	1	33	5		platelets normal	
3/14	4,450,000	86	7000	65	35	5	60	0	31	4		platelets normal	

no appreciable change in the white, red, or platelet count the patient was now able to sit up in a chair. On August 25 the red blood count, hemoglobin, and white blood count fell, and three more transfusions were given even though the patient was feeling better and the bleeding from the gums and nose had stopped. On September 16, 1933, thirteen weeks after admission, the patient was discharged with 1,930,000 red blood cells, 42 per cent hemoglobin, 3,990 white blood cells, and 47 per cent polymorphonuclears. Although his blood picture did not show complete recovery by any means, he was clinically much improved. At home his private physician placed him on high doses of iron and ventriculin. With this medication, rest and high caloric diet he rapidly regained his former strength. A blood count taken four months after his discharge was normal in every respect, as were blood counts taken six, eight and ten months later. The patient has remained healthy and normal to date, weighs fully 200 pounds and has no complaints at all.

the count falls within two or three days to 20 per cent (or even as low as 12 per cent) of normal. If she gave no injection after the first one, the fall in white blood cells would continue to a level well below the 50 per cent, but later there would be spontaneous and complete recovery. However, if the second injection was given, the count would eventually fall below 12 per cent and recovery failed to take place. The myeloblastic elements, particularly the polymorphonuclears, were found depressed by the benzol. There was no destruction of the white blood cells in the circulating blood, but an inhibition of their formation. Only later with increasing doses was a depressive effect on the other tissues in the bone-marrow demonstrated (red blood cells and platelets).

Translated to human subjects, the primary action of benzol (arsphenamine) is depression of granulocyte formation, this action is early, and can be reversed if no more benzol is administered. However, with continued benzol doses, the later "secondary" actions are permitted to develop and an irreversible situation is brought about. The secondary effects are on the megalokaryocytes, causing not only a reduction in number, but also in quality of the platelets. The hemorrhagic diathesis that results leads to bleeding from the gums, nose, gastrointestinal tract, etc. The red blood cells are thus involved secondarily, suffering in proportion to this bleeding. Since benzol does not affect the red blood cells primarily there are no signs of regeneration—no reticulocytes, or nucleated red blood cells¹⁵. The final, late stage of arsphenamine bone-marrow depression is thus a "panmyelophthisis". If the bone-marrow has simply been depressed, there is some chance of recovery with repeated transfusions that tide the patient over the period of bone-marrow inactivity. Where a true aplasia of the bone-marrow has resulted, however, there appears to be little basis for any such hope. It is not possible to make this differentiation (depression or true aplasia of bone-marrow) from the study of circulating blood alone. It is of the utmost importance prognostically to perform a bone-marrow puncture in these cases. In case 1 a puncture was performed in the first week at the hospital and showed red bone-marrow with about the usual number of young cells, but few mature segmented neutrophils. This depression without aplasia of the myeloid system indicated that there was some bone-marrow tissue left to stimulate with repeated transfusions. The term "panmyelophthisis" we believe describes the condition of functional depression of the bone-marrow better than "aplastic anemia," a term which indicates organic depletion of the bone-marrow. This condition surely did not exist in case 1, and in all probability was not present in case 2, either.

A few words must be said about the clinical course shown by the two cases reported. "Panmyelophthisis" is a relatively late reaction of the body to arsphenamine poisoning and occurs typically several months after the beginning of arsphenamine administration. The "incubation" period is long here when compared with the toxic effects of arsphenamine on the liver

(where symptoms are likely to appear much earlier,—i e, during the first few weeks) This may be because the first symptoms of toxic action of arsphenamine on the bone-marrow are slight, there being only signs of general intolerance of the drug, such as the weakness, nausea and feverishness that case 1 experienced after each injection Moore and Keidel⁷ speak of itching or a fine rash as prodromata The only unmistakable sign of trouble, however, is the neutropenia It cannot therefore be urged too strongly that patients who show any intolerance of, or reaction to, arsphenamine injection should have a blood count performed By this means we can detect the neutropenic cases and stop administering the drug before irreversible damage has occurred Our therapeutic desideratum is to recognize intolerance of the bone-marrow to arsphenamine before a hemorrhagic diathesis or an aplastic anemia has set in By constant vigilance for the advent of neutropenia, we can recognize these cases early enough to stop the progress of the disease to the fully developed "panmyelophthisis," which, spite of the best of treatment, is fatal in about 80 per cent of the cases¹³

At the stage when the disease is confined to the leukoblastic tissues (the first or "neutropenic" stage) the nucleotide administration as sponsored by Jackson¹⁶ may reasonably be given a trial In the later stages of panmyelophthisis, as in our two cases, nucleotide injection appeared to have no appreciable effect on the white blood cells The treatment is preferably the use of persistent transfusions until death or recovery supervenes

SUMMARY AND CONCLUSIONS

Two cases of complete bone-marrow depression several months after arsphenamine administration are reported An individual constitutional susceptibility of the bone-marrow to the toxic agent may explain the occurrence of this relatively rare disease In mode of onset, blood pictures and clinical characteristics such cases resemble very closely those due to chronic benzol poisoning Although there is no definite proof, it is likely that the benzol ring into which the arsenic is substituted in arsphenamine is responsible for the blood dyscrasias here described, and not the arsenic The relatively benign hemorrhagic diathesis occurring shortly after an injection of arsphenamine due to an "anaphylactoid" reaction of the thrombocytes is differentiated from the true depression of the bone-marrow caused by the slow accumulation of the toxin (benzol) and resulting in bone-marrow depression weeks and months after the administration began A study of bone-marrow depression in chronic benzol poisoning, and after arsphenamine administration indicates that the toxin most often shows an early affinity for the leukoblastic tissue in the bone-marrow Thus, the early, easily reversible action of arsphenamine on the hematopoietic system is most often a reduction in the white blood cells, particularly the polymorphonuclears Clinically this is expressed as a neutropenia associated with signs of lowered resistance—weakness, persistent colds, numerous smaller infections

tions, etc. If this early neutropenic stage is recognized and the arsphenamine administration stopped, the patient may be spared the later and frequently irreversible effects on the bone-marrow of the accumulating arsphenamine (benzol).

Reduction in the number and quality of the platelets, with consequent bleeding from the mucous membranes of the nose, mouth, gastrointestinal tract, etc. is more likely to be a later than an early effect. The bleeding alone explains the marked secondary anemia that finally occurs in most cases, although a direct depression of the erythroblastic tissues may be the cause of the erythrocytopenia in some. Thus the final, often irreversible, stage of the toxic action of arsphenamine (benzol) is a depression to a varying degree of all the elements of the bone-marrow. If puncture reveals a bone-marrow which is not aplastic, blood transfusions persisted in for many weeks may tide the patient over the period of temporary marrow inactivity, and lead to permanent recovery, as in the two cases reported. If a true aplasia of the bone-marrow has already resulted, however, the outlook is practically hopeless. The prognostic importance of bone-marrow puncture in this connection cannot be overemphasized. In any case, persistently repeated transfusions, no matter how ill the patient appears clinically, offer the only hope at this late stage of the disease, and are, therefore, always indicated in its treatment.

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BACILLUS FRIEDLANDER INFECTIONS¹

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IN the minds of most physicians and in almost all textbooks on bacteriology and clinical medicine, *B friedlander*¹ is associated with pneumonia and other infections of the respiratory tract. This traditional viewpoint is responsible for the fact that its common synonyms are *Bacillus pneumoniae* and *Pneumobacillus* and that its modern scientific designation according to the Bergey² bacteriological nomenclature is *Klebsiella pneumoniae*. Infections of other parts of the body with this organism are generally regarded as relatively less common.

Our bacteriological experience with 198 *B friedlander* infections is recorded because it contradicts this conception of the predominant rôle played by the organism in infections of various parts of the body. The observations to be reported in this paper, and a critical review of medical literature of the past 75 years, demonstrate that the respiratory tract and especially the lung is actually one of the less common sites of primary infection and that the current terminology serves to perpetuate a wrong emphasis concerning the usual portal of entry and the essential rôle of the organism in infections.

Friedlander discovered his encapsulated gram-negative bacillus in 1882 in spreads made post mortem from the lungs of eight patients who had died of pneumonia. For some four years thereafter it was generally regarded as the cause of pneumonia, until Weichselbaum's³ report upon the *Diplococcus pneumoniae* in 1886. Although Weichselbaum's observations upon 129 cases established the pneumococcus as the cause of lobar pneumonia, and minimized the relative importance of *B friedlander*, he observed the bacillus in microscopic spread in nine cases, isolated it in mixed cultures in six and in pure culture in three instances. He and Netter⁴ are widely quoted as accepting it as a less frequent cause of lobar pneumonia and bronchopneumonia because they found it in 7 or 8 per cent of their cases. It seems to have escaped notice that their observations as well as the reports of subsequent observers who confirmed their statistics were based upon postmortem bacteriology and, judged by more modern standards, are therefore of doubtful value. Bacteriological experiences reported on large numbers of cases during and subsequent to the World War indicate that *B friedlander* is encountered relatively rarely in pneumonia.

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Many authentic Friedlander bacillus infections of the lungs and other parts of the respiratory tract have been recorded in the literature, but in most instances it is obvious that the observer is reporting what is undoubtedly a rarity in his experience. Unfortunately, some of the recorded cases are unconvincing because they are based solely upon postmortem culture of the organism from a pneumonic lung or other tissue. Some represent influenzal pneumonia with a secondary invasion with *B. friedlander*. Others are chronic lung abscesses with mixed infections, or tuberculous cavitations with secondary *B. friedlander* infections. Still other cases are metastatic lung abscesses from a primary focus of infection within the abdomen. A case of lobar pneumonia recently reported by Bensley⁵ seems to us to have been due to pneumococcus type II and the *B. friedlander* invaded the blood stream only preagonally. Two of the largest and best described groups of *B. friedlander* pneumonia were reported recently by Solomon⁶ from Bellevue Hospital and by Bullock⁷ from the Harlem Hospital, New York.

It is beyond the scope of this paper to review the voluminous literature upon this organism, except to state that it has been found in almost every part of the body. Yet almost every textbook of bacteriology and clinical medicine continues to lay stress upon its relationship to pneumonia and most of them state specifically that it may cause a severe, often fatal, but rather rare form of the disease. They usually mention some of the other sites of infection (Zinnser,⁸ Jordan,⁹ Park, Williams and Krumwiede,¹⁰ Topley and Wilson,¹¹ British Medical Research Council,¹² Ford,¹³ Stitt,¹⁴ Zinnser and Bayne-Jones¹⁵).

In this paper we have preferred to call the organism *B. friedlander* in preference to the synonyms which associate it with pneumonia and to such descriptive designations as *Bacillus mucosus capsulatus* and, for a subgroup, *Bacillus acidilactici*. Formerly we did not attempt to differentiate between the various types of Friedlander organisms because of the lack of clear cut bacteriological criteria. More recently Julianelle¹⁶ has divided the *B. friedlander* into three groups, A, B, and C, according to their serologic reactions. Some of the strains were identified serologically by cross agglutination with pneumococcus type II serum (Avery, Heidelberger, and Goebel¹⁷). The classification by Julianelle is being followed closely in our laboratory, but sufficient information is not yet available regarding the pathogenicity of the various types. For this reason, gram-negative bacilli showing well defined capsules and typical "gum drop" and stringy colonies on solid media were considered to belong to the *B. friedlander* group, provided these characteristics persisted for at least 3 to 4 passages through artificial media. It should therefore be understood that the term *B. friedlander* employed in this report implies the Friedlander group of encapsulated gram-negative bacilli.

RESPIRATORY TRACT

The presence of *B. friedlander* in stained spreads made from the sputum or the lung of a patient with pneumonia probably rarely escapes detection. Because of the traditional association of this gram-negative bacillus with pneumonia, its observation anywhere in the respiratory tract usually results in its prompt identification by means of the capsule stain.

On the other hand, so strong is the influence of medical tradition that gram-negative bacilli encountered in the intestinal tract or in the biliary or urinary passages are apt to be associated with the colon-typhoid group of bacteria and to be inoculated for identification upon the various sugar media. Unfortunately, many strains of *B. friedlander* and of *B. coli* form acid and gas in identical sugar media. Unless a capsule stain is made or attention is attracted by the mucoid character of the surface growth on solid media, observations upon sugar media may result in confusing the organism with the colon group. We can conceive of no better explanation for the conspicuous attention which *B. friedlander* continues to receive in bacteriological observation upon respiratory tract infections and the relative neglect of the more important rôle played by this organism in infections of the abdominal cavity.

In reporting cases of primary *B. friedlander* pneumonia, it is important to exclude the following:

- 1 Secondary invasions (often pyaemic) in cases of primary pneumococcus pneumonia
- 2 Influenzal pneumonia with secondary invasion of the affected lung by *B. friedlander* and a variety of other organisms
- 3 Chronic bronchiectases, lung abscesses and tuberculous cavitations in which a secondary *B. friedlander* infection has occurred
- 4 Metastatic infections of the lung from a primary focus of *B. friedlander* infection within the abdomen

In the authentic cases of *B. friedlander* pneumonia, the cut surface of the consolidated lung may appear peculiarly mucoid. Microscopically, the exudate in the alveoli presents a more mucinous appearance than the usual pneumonic lung and may contain large numbers of encapsulated gram-negative bacilli. The organisms may also be present in large numbers in the interalveolar capillaries.

TABLE I
Bacillus Friedlander Infections
198 Cases

Site	Number of Cases	Mortality	Bacteremia	
			No	Died
Gastrointestinal tract	61		1	1
Genito-urinary tract	50	8 (16%)	6	3
Biliary passages and liver	46	14 (30%)	6	5
Lungs and upper respiratory tract	25		1	1
Miscellaneous: skin, meninges, etc.	10		1	1
Vagina, uterus and adnexa	6		1	1

In our series of 198 infections, we have had only two cases of pneumonia in which the clinical and bacteriological evidence during life left no doubt that *B. friedlander* was the primary cause of the pulmonary infection. The rarity of primary Friedlander pneumonias is indicated by the fact that these are the only two proved cases observed at the Mount Sinai Hospital, New York, during a period of 36 years. In seven other cases of lobar or bronchopneumonia, *B. friedlander* was recovered from the sputum or lung during life in association with pneumococci or streptococci.

The organism was also recovered occasionally from pneumonic lungs at necropsy in association with other bacteria, usually pneumococci or streptococci. It may therefore have been a secondary invader or a postmortem contamination. Our experience leads us to believe that *B. friedlander* may at times gain entrance into the body preagonally from the intestinal tract. Postmortem spreads and cultures from pneumonic lungs are therefore of little value.

Other Infections of the Respiratory Tract. Aside from the nine cases of pneumonia, of which only two are primary infections, the organism was isolated 16 times from other infections of the respiratory tract during life. The cases were as follows:

Pharyngitis	1
Acute otitis media and mastoiditis	3
Chronic otitis media	1
Suppurative sinusitis	3 (one with meningitis)
Thornwald abscess of the nasopharynx	1
Infected thyroglossal cyst	1
Submental abscess	1
Pleural effusion of cardiac origin	1 (contamination)
Pleurisy with effusion	1 (probably a contamination)
Chronic lung abscess	1
Empyema thoracis	2 (one probably a contamination)

One of the cases of mastoiditis developed a *B. friedlander* meningitis and a bacteremia.

The nine cases in which the organism was isolated from an infection in the nasopharynx, the sinuses or the ears contrast numerically with the 163 *B. friedlander* infections of the abdomen, of which 61 were due to perforative lesions of the intestines.

The organism is occasionally encountered in the normal flora of the upper respiratory tract and is undoubtedly responsible at times for infections in the sinuses and the ears. Because of the much greater frequency of its occurrence in the intestinal tract, our experience inclines us to regard its occasional presence in the upper respiratory tract with suspicion as a possible contamination, or as a secondary invader. Even when found repeatedly in pure culture from infected sinuses or ears, it may have been introduced by previous instrumentation.

Dr. Lee Hurd¹⁸ has recently called attention to the fact that 25 years ago *B. friedlander* infections of the upper respiratory tract, the sinuses and the ears were not such rarities as they are today. Comparative statistics of

25 years ago and of today reveal a striking diminution in the frequency of this type of infection. The use by many of the pioneer specialists of unsterile instruments with unsterile hands may possibly have been the means of causing secondary infections of the ear, nose and throat by the introduction of *B. friedlander* and other organisms derived from the intestinal flora. Since the universal introduction of modern aseptic technic into otolaryngologic practice, these bacteria are rarely encountered in infections of the upper respiratory tract.

The occurrence of *B. friedlander* in ozaena and rhinoscleroma is now generally regarded as a secondary invasion of no causal significance. We venture to suggest that the organism has been introduced in these cases from the intestinal tract by nose picking, a habit almost irresistible in this type of nasal trouble.

INTESTINAL TRACT

B. friedlander is commonly found in the intestinal tract. It has been isolated from the stool in some cases of enteritis (Berthelot and Bertrand,¹⁹ Jampolis, Howell, Calvin and Leventhal,²⁰ Abel,²¹ Zinnser⁸). We have made no systematic effort to determine the frequency of the encapsulated gram-negative bacilli in the intestinal flora, but Dudgeon²² has found it in the feces of 55 per cent of normal and abnormal individuals. Kendall²³ regards *B. friedlander* as an almost constant habitant of the intestinal tract of nurslings, common in the intestinal contents of bottle fed infants and frequently present in small numbers in the adult intestinal tract.

It is, therefore, not surprising that we encountered the Friedlander bacillus most frequently in infections arising primarily from the intestinal tract. In most instances the intraabdominal infection was due to a perforative lesion of the intestine or the appendix. We are able to report 61 cases of this type. The number was limited only by the fact that cultures were usually omitted by the surgeons in intraabdominal suppurations due to perforations of the appendix or other parts of the intestinal tract.

Of the 61 instances in which the intraabdominal suppuration was apparently due to this organism, 53 were appendicitis abscesses. In 16 instances, it was associated with one or more other organisms characteristic of the intestinal flora, most frequently *B. coli*. The organism was also recovered in subphrenic collections of pus and in peritonitis of appendiceal origin, peritonitis complicating an intestinal obstruction, peritonitis due to a perforating carcinoma of the cecum, pelvic abscess secondary to a sigmoid diverticulitis with vesico-sigmoid fistula and perirectal abscess. In spite of the irregularity with which cultures were made in abdominal infections of intestinal origin, our experience indicates that *B. friedlander* is far more commonly encountered in infections arising from perforative lesions of the intestinal tract, particularly the appendix and large intestine, than in infections of any other organ.

BILIARY TRACT

Cholecystitis and Cholangitis Friedlander infections of the gall-bladder and bile passages and liver abscess due to this organism have been recorded by Carnot, Dumont and Lebert,²⁴ Brouardel,²⁵ Hegler and Nathan²⁶ and others. In contrast to the relative rarity of respiratory tract infections due to *B. friedlander*, we are able to report 46 cases of suppurative infections of the biliary tract. The pus in the infected gall-bladder or common duct is usually thin and presents no distinctive characteristics. In some instances it is thick and mucoid and has a faint foul odor. Gangrene of the gall-bladder wall and pericholecystic abscesses are observed as in other types of infection.

B. friedlander was present in the pus in pure culture in 43 of the 46 cases of cholecystitis and cholangitis. In two instances it was associated with *B. coli* and in one with *B. coli* and *B. proteus*.

Mechanical Predisposing Causes Gall stones were present in the gall-bladder or common bile duct in 38 of the 46 cases. In two other instances, the common or cystic duct was obstructed by carcinoma. It is of interest to note that *B. friedlander* infection of the gall-bladder or biliary passages occurred without any obvious predisposing cause only in six cases in the entire series. This suggests that the excretion of the organism by the liver, whenever it gains entry into the portal circulation, is usually accompanied by little danger of infection of the biliary passages—unless there is biliary stasis due to a mechanical cause such as calculus or neoplasm.

Mortality Our observations reveal a strikingly high mortality for biliary tract infections with this organism. Fourteen of the series of 46 patients died, a mortality of 30 per cent. This extremely high mortality was due in part to the unusually frequent occurrence of cholangitic and pylephlebotic liver abscesses, secondary to the infection of the gall-bladder or biliary passages.

Liver Abscess In 10 of the 14 fatal cases one or more liver abscesses were revealed by operation or necropsy. In four, the liver abscesses were due to an ascending suppurative cholangitis. Two were produced by direct extension from the infected gall-bladder or the associated pericholecystic abscesses. Four were of pylephlebotic origin. The suppurative pylephlebitis arose in three of the cases as a result of the suppuration in the gall-bladder and common bile duct. In one case, a pylephlebotic liver abscess was secondary to an acute gangrenous appendicitis. Except for this one instance, all cases of liver abscess due to *B. friedlander* developed as a result of a primary infection in the gall-bladder or biliary passages.

In five of the 10 cases, the liver suppuration gave rise to a bacteremia, a remarkably high incidence. In three of these cases, necropsy revealed that the organisms had gained access to the blood stream because of a secondary suppurative phlebitis of an hepatic vein adjacent to the abscess.

Metastatic Lung Abscesses Multiple lung abscesses were present as a

complication in three of the cases complicated by liver abscess, in two of which the blood culture was positive. One of the cases of metastatic lung abscess developed an empyema of the pleura which required thoracotomy. In a case of suppurative pyelophlebitis of the right portal vein and subphrenic abscess a pleural effusion developed in the right pleural cavity, which became infected only after transpleural aspiration of the subphrenic abscess. Thereafter, a pure culture of *B. friedlander* was obtained from the pleural cavity.

When *B. friedlander* is cultured from a lung abscess or an empyema of the pleura, the possibility must be considered that the abscess of the lung or pleura may be metastatic from a primary suppuration of the liver.

URINARY TRACT

The organism has been repeatedly described as the cause of infections of the genito-urinary tract (Chiari,²⁷ Park, Williams and Krumwiede,¹⁰ Villiere,²⁸ Bertrand-Fontaine and Parlier,⁹ Montt-Saavedro,¹⁰ Howard,³¹ Macaigne,³² Speck,³³ Halban³⁴). In our experience the *B. friedlander* infections of the genito-urinary tract are somewhat more frequent than those of the gall-bladder, liver and biliary passages. We are able to report upon 50 infections of the urinary tract, compared with 46 cases of infection of the biliary tract. Although the *B. friedlander* is usually found in the liver and biliary tract infections in pure culture, it is more commonly observed in the infections of the kidney and the urinary passages in association with *B. coli*, *B. alkaligenes*, *B. pyocyaneus*, or the enterococcus. Like *B. friedlander*, they are derived primarily from the intestinal flora. Mixed infections with one or more of these organisms were present in 13 of the 50 cases. In one of the cases the blood as well as the urine contained both *B. coli* and *B. friedlander*.

TABLE II

Mechanical Obstruction as a Predisposing Factor in Excretory Infections with <i>B. friedlander</i>		
Biliary passages and liver	Total number of cases	46
Stones in common duct or gall-bladder		38
Neoplasm obstructing common duct		2
No obstruction		6
Urinary tract	Total number of cases	50
Stones in urinary tract		37
Obstruction due to carcinoma of the bladder		1
Obstruction due to adenoma of the prostate		2
Mixed infection in tuberculosis of kidney		2
Horseshoe kidney		1
Kinking of uretero-pelvic junction		1
No obstruction		6

Predisposing Causes. As in the biliary infections, mechanical stasis in the urinary passages was a common predisposing factor, being present in 44 of the 50 cases. Although in the biliary tract the cause of stasis was either calculi or neoplasm, in the urinary tract infections a greater variety of mechanical causes played a rôle. Urinary calculi were by far the most com-

mon contributory cause, but other factors were carcinoma of the bladder in one case, adenoma of the prostate in two, tuberculosis in two, horse shoe kidney in one and kinking of the uretero-pelvic junction in one case. Apparently the organism is excreted by the kidneys whenever it gains entry into the systemic circulation, but even under these circumstances it is not apt to cause an infection in the urinary passages unless there is urinary stasis due to a mechanical obstruction.

Mortality The mortality rate of *B. friedlander* infections of the urinary tract is lower than that of similar infections of the liver and the biliary passages. Eight of the 50 patients died of the infection, a mortality of 17 per cent, compared with a death rate of 30 per cent in our biliary series. In three of the eight patients who died, the blood culture was positive during life. However, two patients recovered who had a single positive blood culture during the course of their urinary infection and a third patient recovered although blood culture had been positive on two occasions.

FEMALE GENITAL TRACT

Uterine and tubal infections with this bacterium have been reported by Scheyer³⁵ and Howard³¹ and cases of postabortive sepsis by Reichert³⁶. Our experience is limited to five cases of suppurative salpingitis or salpingo-oophoritis complicated by pelvic abscess from which a pure culture of the organism was recovered, and to one case of recto-vaginal fistula following colpotomy. It is reasonable to believe that the infection in some of these cases spread to the uterus and adnexa from the adjacent rectum or colon. In one case of postabortive infection, the organism was probably introduced during instrumentation by contamination with fecal material.

B. FRIEDLANDER BACTEREMIAS

The literature contains many reports of cases of Friedlander bacteremia (Lenhartz,³⁷ Canon,³⁸ Clairmount,³⁹ Chiari,²⁷ Conradi,⁴⁰ Caussade, Joltram and Surmount,⁴¹ Beco,⁴² Apelt,⁴³ Wehrsig,⁴⁴ Mason and Beattie,⁴⁵ Colombe,⁴⁶ Lereboullet and Denoyelle,⁴⁷ Lereboullet and Pierrot,⁴⁸ Breitkoff,⁴⁹ Sisson and Thompson,⁵⁰ Belk⁵¹). In Hegler and Nathan's²⁶ and Courmount, Dujol and Devic's⁵² cases, the portal of entry was an infection of the gall-bladder or bile passages, in Chiari's²⁷ case an ascending suppurative nephritis, in Conradi's⁴⁰ an umbilical vein infection and in one of Lereboullet's⁴⁸ three cases we suspect the urinary tract. In some of the reported cases, the portal of entry for the bacteremia was not ascertained during life (Abel⁵¹).

Libman⁵³ obtained positive blood cultures only three times among over 40 cases of suppurative pyelophlebitis and in one of the three instances, the bacteremia was due to *B. friedlander*. On the other hand, the organisms which he encountered most commonly in the blood stream in cases of pyelo-

nephritis arising without any antecedent manipulation in the genito-urinary tract were the colon bacillus and the Friedlander bacillus. He emphasized the fact that the latter is at times mistaken for the colon bacillus, because a proper capsule stain necessary for its identification is not employed.

Cases of *B. friedlander* bacteremia with recovery have been described by Courmont, Savy and Charlet,⁵⁴ Mitchell⁵⁵ and others. Crohn⁵⁶ reported a case of acute *B. friedlander* endocarditis, the portal of entry being a pyelitis, and Schoeppler⁵⁷ described a case of pericarditis.

We can report 16 cases of *B. friedlander* bacteremia, of which four recovered. A fifth case recovered from the bacteremia only to return to the hospital subsequently with a secondary (*B. friedlander*) osteomyelitis of a vertebra from which he died. In 14 cases the organism was present in the blood during life in pure culture, in one it was associated in the blood with *B. coli* and in another with several intestinal bacteria.

Portals of Entry. Of the 16 cases of *B. friedlander* bacteremia, six are from infections of the liver and biliary tract, six from infections of the urinary tract, one from an acute otitis media complicated by mastoiditis and suppurative meningitis, one from a postoperative meningitis probably due to fecal or skin contamination during convalescence from an operation for spinal cord neoplasm and one from an infection of the gynecological tract.

In one other case, the organism was recovered in a blood culture from a patient with aplastic anemia only two and a half days before death. The blood culture also contained colonies of *Staphylococcus albus* and *Streptococcus alpha* so that we are probably justified in concluding that this case represented a preagonal blood invasion in a patient dying slowly of a wasting and debilitating disease.

It is of particular interest to note that no case of bacteremia in our entire series had its origin in a primary lung infection and only one in the upper respiratory tract (otitis and mastoiditis). However, others have reported instances of *B. friedlander* bacteremia complicating pneumonia.

In the case of bacteremia which followed an ear infection, there was doubt (1) whether *B. friedlander* had gained access to the ear as a result of an acute nasopharyngitis and sinusitis, or (2) whether some other organism has been the primary infective agent in the otitis and the *B. friedlander* had been introduced secondarily at the time of the myringotomy, 10 days after the onset of the otitis. The mastoiditis developed four days after the myringotomy. Signs of meningitis began almost four weeks later and the patient died of this cause within another week.

BACTEREMIA COMPLICATING LIVER AND BILIARY TRACT INFECTIONS

Six cases of bacteremia were observed among 46 *B. friedlander* infections of the liver and biliary passages. Five died of the infection. One recovered and was reported to be well four months after discharge from the hospital.

It is important to note that multiple abscesses of the liver were found at necropsy in all five of the fatal cases. In two the liver abscesses were pyelephlebitic and in the other three cholangitic or cholecystic in origin. In the patient who recovered, the liver at operation seemed clinically to be normal. A cholecystitis and cholangitis was found and drainage of the gall-bladder was followed by recovery from the blood stream infection.

In three of the six cases of liver abscess with bacteremia, the organism gained access to the general circulation only after the development of a suppurative thrombophlebitis of adjacent hepatic veins.

In all six cases of bacteremia complicating liver and biliary tract infections, the organism was excreted by the kidneys and could be recovered from the urine. Five developed secondary excretory Friedlander infections of the urinary tract.

BACTEREMIA COMPLICATING INFECTIONS OF THE URINARY TRACT

In our experience, bacteremia due to *B. friedlander* arises as frequently from infections of the kidney and urinary passages as from the biliary tract. This complication occurred in six of our 50 cases of *B. friedlander* infections of the kidneys or urinary passages.

Fortunately, blood invasions from this source are often transient, so that three of our six cases recovered. In two of the recovered cases, the organism was recovered from the blood stream only on the day following a so-called urethral or ureteral chill.

In one of the three fatal *B. friedlander* bacteremias of renal origin, the blood stream infection cleared up spontaneously so that the patient was discharged from the hospital apparently cured. This is the patient previously mentioned who returned eight weeks later because of a metastatic osteomyelitis of a vertebra and died of a secondary *B. friedlander* bacteremia from this source.

BACTEREMIA FROM INTESTINAL TRACT INFECTIONS

In spite of the fact that the *B. friedlander* is a normal habitant of the intestinal tract and that it is found most commonly in pyogenic infections of the abdominal cavity due to perforative lesions of the intestines and appendix, it rarely enters the blood stream from this site. In one instance in our experience, which we have already mentioned, it entered the blood stream preagonally two and a half days before death in a patient dying of aplastic anemia.

SUMMARY

The Friedlander group of encapsulated gram-negative bacilli usually gain entry into the body from the intestinal tract. For this reason they are frequently encountered in abdominal suppurations due to perforative lesions of the appendix and the colon.

Like *B. coli* and other intestinal saprophytes *B. friedlander* may enter the systemic or the portal circulation and be excreted by the kidneys or the liver. Under these circumstances, excretory infections are apt to occur if there is stasis of urine or bile due to the presence of a calculus, a neoplasm or other mechanical factor. A predisposing mechanical factor was present in 84 of the 96 cases of excretory infections of the urinary and the biliary passages.

The mortality of *B. friedlander* infections of the abdominal viscera is high. There were eight deaths among 50 urinary tract infections (16 per cent) and 14 deaths among 46 infections of the biliary tract (30 per cent). The isolation of *B. friedlander*, especially from infected bile, is therefore of grave prognostic import.

In urinary tract infections, *B. friedlander* is often associated with *B. coli*, *B. proteus*, *B. pyocyaneus*, enterococcus or other bacteria belonging to the intestinal flora. In biliary infections this association is uncommon and the organism is usually recovered in pure culture.

B. friedlander is encountered infrequently in infections of the vagina, uterus and female adnexa, to which it may gain access by direct extension or by lymphatic or hematogenous carriage from the intestinal tract. In some instances it is probably introduced as a contamination from the adjacent rectum or anus by instrumentation or during self induction of abortion.

Primary *B. friedlander* infections of the lungs and the upper respiratory tract are clinical rarities, in comparison with the frequency of infections of the abdominal viscera.

Sixteen cases of *B. friedlander* bacteremia are reported, of which 12 developed from infections of the biliary or the urinary tract. Most of the cases of bacteremia which arose from extrarenal sites of infection developed a secondary excretory infection of the urinary tract during their clinical course. Recovery was common in the bacteremias of renal origin, and unusual in blood infections arising from the liver and biliary tract and other extrarenal sites.

CONCLUSIONS

This report of 198 *B. friedlander* infections indicates that the organism is predominantly associated with abdominal infections, especially suppurations due to perforations of the appendix and colon, and next most frequently with excretory infections of the biliary and the urinary tract. In this respect it conforms pathogenically with *B. coli* and other gram-negative bacilli of the intestinal flora. In comparison with the frequency of Friedlander infections of the abdominal viscera, infections of the respiratory tract with this organism are relatively uncommon.

It is therefore recommended that the terms *Bacillus pneumomae* and *Pneumobacillus* be abandoned because they have served to perpetuate a

wrong conception of the essential rôle of the bacillus of Friedlander in infections, and that the bacteriological designation *Klebsiella pneumoniae* be changed to *Klebsiella Friedlanderi*

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THE BLOOD PRESSURE IN STENOSIS AT THE ISTHMUS (COARCTATION) OF THE AORTA, CASE REPORTS

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IT is well known that the arterial pressure in the arms in cases of congenital stenosis at the isthmus of the aorta is frequently higher than the normal. This is so often the case, that the impression is more or less current that hypertension in the arms is a necessary part of the diagnostic picture, and that investigation of all cases of hypertension will lead to recognition of all cases of isthmus stenosis. Gossage³⁴ has said "No doubt in these cases the blood pressure is always high, so as to overcome the difficulty of getting the blood through the narrow arterial channels." Lewis,⁷⁷ referring to instances of slight constriction and to cases of coarctation complicated by cardiac embarrassment, is of the opinion that "if we note these cases as natural exceptions then it is true to state that most cases, perhaps all uncomplicated cases, of coarctation of the aorta of the adult type present high blood pressure, the statement applies to both systolic and to so-called diastolic readings."

That such views are in accord with the facts in a large proportion of the cases is readily demonstrated. My own experience is perhaps rather typical of 12 original cases which I have examined, there was an absolute hypertension in the arms in 10, the pressure was not determined in one, while in another it was normal (last case in the series herewith reported). The occasional occurrence of such findings as those in case 5, in which the pressure in the arms, while higher than that in the legs, is nevertheless within normal limits, together with some interesting findings among the cases already reported, will suggest a modification of the general opinion that the finding of hypertension affords the most important clue to isthmus stenosis.

In order to determine the significance and relative incidence of normal blood pressure in coarctation, I have reviewed the literature and have analyzed all the pressure readings that are accessible. With this analysis, I shall report briefly five heretofore unreported cases, including that of the patient with normal pressure.

The first blood pressure readings in this condition seem to have been made by Potam and Bureau⁷⁸ in 1892, followed in 1893 by an observation by Steiner.⁹¹ At the present time 170 such reports have been found.

Blood pressure reports divide themselves into four general categories. The first group consists of those cases in which hypertension was demon-

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strated in both arms, the second group contains cases in which hypertension was reported but in which the pressure was determined from one arm only. Doubtless a number of cases of this type would have been found to have elevated pressure in both arms, had a more complete report been given, hence would have appeared in table 1. However, there is a group (table 4) in which there was a hypertension in the right arm, with normal pressure in the left because of the possibility that some cases in table 2 might have been of the same type as the cases in table 4 or table 1 if the pressure had been determined in both arms, it seems safer to leave all cases of unilateral pressure reports in a separate group (II).

Tables 1 and 2 consist of cases with the more orthodox pressure findings—a definite hypertension in one or both arms and comparatively low pressure with feeble pulsations in the legs.

Of the adult hypertensive patients in table 1 the average pressure in the right arm was found to be 190 systolic and 92 diastolic, that in the left arm 185 systolic and 94 diastolic. Such a difference has been noted in previous reports and has been thought to be due to slowing of the blood stream as it passes the mouth of the left subclavian artery, a condition due to the proximity of the coarctation to the left subclavian. The average pressures in the legs were not unlike, being 125 systolic and 93 diastolic in the right, 120 systolic and 89 diastolic in the left (table 1).

In table 4 is found a group of cases of unusual interest inasmuch as there is a marked disparity of pressure in the two arms, that of the left being within normal limits. This statement should be qualified by pointing out that there was a diastolic hypertension in the left arm in four of the 10 cases of table 4. Moreover, the case reported by East²¹ (number 5) is an exception to all rules, since the pressure is substantially higher in the left arm than in the right. As there was no autopsy, the explanation of this bizarre finding is not known.

A possible interpretation of the other nine cases of table 4 is suggested by Parkes-Weber and Knop²¹ in discussing the case of Turkington²⁰ (number 8 in this group). These authors quote D. E. Bedford, who described a case in the Museum of the Heart Hospital, London, in which there was observed a fibrotic stenosis at the origin of the left subclavian artery.

It seems probable that the cases in table 4, excepting that of East²¹ (number 5), had an isthmus stenosis complicated by involvement of the mouth of the left subclavian artery in a stenosing process. In cases of "persistent isthmus" the mouth of the artery and the isthmus might well be involved in a single anomaly.

The cases in table 3 deserve especial note, as here are 19 cases in which the arm pressure was within normal limits. I have included my own observation (case 5 in the appended series). Nine cases were substantiated by autopsy. It should be stated that no note was found in some of

CASES OF COARCTATION OF THE AORTA FROM 1892 TO 1936, WITH BLOOD PRESSURE READINGS

TABLE I
Blood Pressure 140 (S) or More in Each Arm

No	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
1	Baker, T W and Shelden, W D	F	25	R 182/82 L 176/74	R pop 118/- L pop 128/-	W	No
2	Blackford, L M	M	30	R 200/110, 158/100 L 180/-	R 120/- L 135/-	W	No
3	Blackford, L M	M	16	R 164/56 L 162/62	R 80/60	W	No
4	Blackford, L M	M	16	R 180/100, 160/76 L 165/100, 156/82	R 108/60	W	No
5	Blackford, L M	M	46	R 158/96 L 154/98	R 102/80 L 106/88	W	No
6	Blackford, L M	F	16	R $\frac{180}{86}$, $\frac{206}{90}$, $\frac{176}{104}$ L 172/102	R 90/60	W	No
7	Blackford, L M	F	22	R 168/84 L 164/90	R 102/88 L 98/84	W	No
8	Brown, J W	F	30	R 180/20 L 150/20	100/-	W	Yes
9	Carnett, J B and Howell, J C	M	75	R 180/80 L 160/80	R 140/96 L 100/80	W	No
10	Codvelle and Henri	M	21	R 230/120 L 230/120	R 120/90 L 120/90	W	No
11	Eppinger, E C and Midelfart, P A H	M	33	R 150/80 L 154/90	R pop 122/94 L pop 120/90	W	No
12	Eppinger, E C and Midelfart, P A H	F	28	R 300/125 L 290/130	R 135/100 L 110/90	W	No
13	Eppinger, E C and Midelfart, P A H	F	32	R 140/90 L 152/120 2 mos before R 116/88 L 135/90	R pop 102/88 L pop 100/88 2 mos before same as above	W	No
14	Evans, W	M	23	R 165/95 L 155/95	145/-	W	No
15	Finesilver, B	M	26	R 230/110 L 150/110	R 120/98 L 105/80	W	Yes
16	Flexner, J	M	19	R 238/128 L 238/128 On subsequent occasions R 178/90 L 178/90	96/72 at time of latter brachial reading, but no pop readings could be obtained consequently upon repeated attempts	W	No

TABLE I—*Continued*

No	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
17	Follet and Caille, E	M	17	R 210/120 L 210/120	R 110/90 L 115/95	W	No
18	Gasser, R R	M	20	3 readings in $\frac{1}{2}$ hr 208-190-210 116-118-120	"Hypotension or inability to record pressure in lower extremities"	W	No
	Subsequent observations by J T King	M	20	R 160/110 L 156/120	R 142/136 L 140/136 Both pop barely audible		
19	Grollman, A and Ferrigan, J P, Jr	M	25	R 162/81 L 176/98	R 109/80 L 113/78	W	Yes
20	Hamilton, B E and Stewart, C C, Jr	M	18	R 170/84 L 170/84	95/-	W	No
21	Hampson, A C	M	12	R 145/75 L 145/75	88/-	W	No
22	Hesdorffer, M B	M	18	R 180/80 L 190/90	100/80	W	No
23	Hodann, C	M	44	R 170/60 L 165/50	R 120/-	W	No
24	Hunter, D	M	14	R 165/90 L 155/85	none taken	W	No
25	King, J T, Jr	M	35	R 180/106 L 180/98	R 110/- L 110/-	W	No
26	King, J T, Jr	M	58	R 210/85 L 160/85 2 wks later R 170/78 L 155/70	R 142/80 2 wks later L 102/90(?)	W	No
27	King, J T, Jr	F	40	R 168-210 80-107 L 173-230 85-120	R 140-162 75-110 L 120-150 72-110	C	No
28	King, J T, Jr (Courtesy of Drs Garis and Conley, Union Memorial Hospital)	F	18	R 180/106 L 195/130	No definite determinations could be made in leg	W	No un-published
29	King, J T, Jr (Courtesy of Drs Fitcher and Padget, Johns Hopkins Hospital)	M	15	R 174/94 L 142/90	R 100/70 L 100/70	W	No un-published

TABLE I—Continued

No	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
30	King, J T, Jr (Courtesy of Dr Henry M. Thomas, Jr, Hospital for the Women of Md)	F	24	R $\frac{160-210}{90-110}$ L $\frac{160-210}{90-110}$	$\frac{110-140}{70-80}$	W	No Un- pub- lished
31	King, J T, Jr	F	22	R 180/102 L 180/102	110/-	W	No Un- pub- lished
32	King, J T, Jr	F	33	R 160/90 L 160/100	85/80	W	No
33	Laffont and Laffargue	F	42	R 230/65 L 230/65	90/60	W	No
34	Laubry, C and Marre, L	M	29	R $\frac{215-220}{90}$ L 220/90	155/85-90 L 150/90	W	No
35	Laubry, C, Routier, D and Van Bogaert, A	M	42	R 200/130 L 200/130	none in legs	W	No
36	Lian, C, Abaza and Frumusan, P	F	30	R 300/90 L 300/90	140/- lower leg	W	No
37	Iichtenberg, H H and Gallagher, H F	F	12	R 210/170 L 210/170 18 mos later 160/90	never obtained in legs	W	No
38	Machado, J de O and Malheiro, L	F	40	R 350/130 L 350/130 1 wk later R 195/85 L 200/85	R 120/80 L 120/75 1 wk later R 75/55 L 75/50	W	No
39	Machado, J de O and Malheiro, L	F	30	R 190/85 L 190/90 3 yrs before 190/80 (Pachon) both arms	R 150/90 L 140/90 3 yrs before 130/90 (both)	W	No
40	Moncrieff, A	M	6	R 150/100 L 150/100	—	W	No
41	Mussio-Fournier, J -C and Barzantini, J -C	M	18	R 235/90 L 235/90 3 mos later R 160/65	R 120/-	W	No
42	Pierce, W F	M	35	R 14/470 L 14/866	diminished pulsa- tion	W	Yes

TABLE I—*Continued*

No	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
43	Pilod and Huguenot	M	20	R 165/95 L 160/90	R 110/85 L 100/80	W	No
44	Purks, W K and Robert, W P	M	14	R 195/80 L 180/70	unobtainable	C	No
45	Railsback, O C and Dock, W	M	45	R 200/100 L 174/98	R 164/140 L 164/130	W	No
46	Rosler, H	M	35	R 180/90 L 185/70	60/- 1	W	No
47	Shapiro, M J (This case observed since age 6)	M	17	R 178/100 L 170/100 In later article 204/100 (R) 185/100 (L)	Unobtainable in either leg	W	No
48	Strayhorn, W D	F	26	R 170/70 L 170/70	not mensurable	W	No
49	Taylor, E F	M	33	R 162/90 L 152/98	—	W	No
50	Taylor, E F	M	50	R 260/122 L 220/160	R 164/142 L 134/102	W	No
51	Thompson, A P and Lamb, F W	F	5	R 215-175 145-120 L 220-200 190-160	125/- popl	W	Yes
52	Ulrich, H L	M	32	R 210/115 L 220/115 14 mos before R 194/112 L 186/108	R 140/120 L 140/125 14 mos before R 114/- L 124/118	W	No
53	Ulrich, H L	M	23	R 140/82 L 140/78 6 mos before 154-144 96-86	R 104/90 L 104/90 6 mos before unobtainable	W	No
54	Vega Diaz, F	—	—	R 210/110 L 220/120	R 145/80 L 125/95	—	—
55	Vega Diaz, F, Albert, C Irigoyen, A and Suls, E	M	13	R 210/110 L 220/120	R thigh 125/80 L thigh 125/95	W	No
56	Wolffe, J B	F	7	R 206/148 L 145/100 6 yrs before R 180/40 and 170/50	no pulse felt	W	No

CASES OF COARCTATION OF THE AORTA FROM 1892 TO 1936, WITH BLOOD PRESSURE READINGS

TABLE II
Blood Pressure 140(S) or More in One Arm

No	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
1	Arloing, F	M	13	190	—	W	No
2	Assmann, H	M	Young	200/100	120/100	W	No
3	Bargi, L	F	19	180/60	—	W	No
4	Beatty, J F	M	22	R 160/90	Unobtainable	W	Yes
5	Blackford, L M	M	20	R 150/84	R fem 100/—	W	No
6	Blumgart, H L, Lawrence, J S and Ernstene, A C	M	47	164/94	88/76	W	No
7	Blumgart, H L, Lawrence, J S and Ernstene, A C	M	66	171/96	123/—	W	No
8	Bode, O B and Knop, F	M	40	200/80	—	W	No
9	Buday, L	M	50	220/70	Not taken	W	Yes
10	Davies, G F S	M	?	180/90	—	W	No
11	Dock, W	M	45	190/100	Feeble delayed femoral pulse	W	No
12	Dock, W	M	37	"Hypertension"	Delayed femoral pulse	W	No
13	Dock, W	M	25	215/85	Feeble delayed femoral pulse	W	No
14	Edelman, A and Maron, R	M	25	R R 195/45	—	W	No
15	Erdmenger, R	M	24	140/—(in extremis)	—	W	No
16	Evans, W	F	45	L 205/120	R 85/—	W	No
17	Farris, H A	M	11	144/110	Unobtainable	W	Yes
18	Farris, H A	M	19	160/90 7 yrs before 120/80	106	W	No
19	Fray, W W	M	married ?	190/80	—	W	No
20	Giroux, M and Jobin, J B	F	20	220/80	Not taken	W	Yes
21	Gossage, A M	F	53	200-225/100	—	W	No
22	Graybiel, A, Ash- ton, A W, and White, P D	F	29	183/95	100/70 (calf)	W	No

TABLE II—*Continued*

No	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
23	Graybiel, A, Ash- ton, A W, and White, P D	M	24	162/100	85/65 (calf)	W	No
24	Graybiel, A, Ash- ton, A W, and White, P D	F	20	163/100	115/65 (calf)	W	No
25	Graybiel, A, Ash- ton, A W, and White, P D	M	28	177/81	100/65 (calf)	W	No
26	Graybiel, A, Ash- ton, A W, and White, P D	F	33	160/87	95/60 (calf)	W	No
27	Hamilton, W F and Abbott, M E	M	14	150/50	—	W	Yes
28	Hamilton, B E, and Stewart, C C, Jr	F	61	R 160/100	120/- dorsalis pedis Femoral arteries pulsated faintly Pop not made out	W	No
29	Hamilton, B E, and Stewart, C C, Jr	F	32	<u>180 to 210</u> 110	Not more than 100/- above knee	W	No
30	Hamilton, B E, and Stewart, C C, Jr	F	22	R <u>150-206</u> 90-112	80/- popliteal	C	No
31	Hardaway, R M, and Sawyer, H P	M	38	300+	Not taken	W	Yes
32	Hein, G E	M	64	<u>170-180</u> —	—	W	No
33	Hein, G E	M	55	150/110	—	W	No
34	Kovesi, G	M	21	170 (Gaertner)	—	W	No
35	Kovesi, G	F	17	220-230 (Riv Roc) 260-265 R rad during attack	—	W	No
36	Laubry, C, Rout er, D, and van Bogaert, A	M	19	210/70 (wrist)	110/60 (ankle)	W	No
37	Laubry, C, Routier, D, and van Bogaert, A	F	24	140/80 (in course of strep sept)	None in legs	W	No
38	Laubry, C and van Bogaert, A	M	24	1 230/120 2 200/120 3 190/120	130/100	W	No

TABLE II—Continued

No	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
39	Lemon, W S	M	22	185/80 2 mos later 192/72	Could not be re- corded	W	No
40	Lewis, Sir T	M	31	181/123	106 (pop)	W	No
41	Lewis, Sir T	M	63	217/102	133 (pop)	W	No
42	Lewis, Sir T	M	37	215/107	85 (pop)	W	No
43	Lewis, Sir T	M	52	192/97	117 (pop)	W	No
44	Lewis, Sir T	M	61	233/103	135/92 (pop)	W	No
45	Lewis, Sir T	M	41	202/99	120/- (pop)	W	No
46	Lewis, Sir T	M	43	192/89	—	W	Yes
47	Lewis, Sir T	M	49	213/118	—	W	Yes
48	Lian, C , Abaza, and Frumusan, P	F	20	180/70-80 at 15 yrs 160/70 each arm)	100/60 (oscill) at 15 yrs 100/60, each leg	W	No
49	Lian, C , Abaza, and Frumusan, P	M	18	160/60 at 15 yrs 150/70	110/50 (lower leg) 150/80 (base of thigh) at 15 yrs 120/70	W	No
50	Lian, C , Abaza, and Frumusan, P	M	13	170/90	thigh 130/60	W	No
51	Loeper and Marchal, G	M	18	165/100	—	W	No
52	Lommel, F	F	38	190/-	—	W	No
53	Mackenzie, G M	M	5	128/78	—	W	No
54	Maxwell, J	F	33	270/80	100/-	W	No
55	Maxwell, J	M	20	200/110	Too low to be ac- curately re- corded	W	No
56	Maxwell, J	F	34	245/160	Impossible to ob- tain in either leg	W	No
57	Meerseman, F , Bergondi J and Andre	M	21	200/110	100/60	W	No
58	Minkowski	M	23	300/- R radial	—	W	No

TABLE II—*Continued*

No	Author	Sex	Age	Blood Pressure		Color	Autopsv
				Arm	Leg		
59	Moon, R O	M	17	180/—	Pulsation in fem was scarcely perceptible	W	No
60	Moga, A , and Sireteanu, M	M	38	200/120	130-110/—	W	No
61	Moga, A , and Sireteanu, M	M	35	150/90	120/—(max) by oscill	W	No
62	Moga, A , and Sireteanu, M	F	30	170/— (max) oscillometer	130/— (max) oscillometer	W	No
63	Parkes-Weber, F	M	40	200/85	—	W	No
64	Parkes-Weber, F and Price, F W	F	56	230-290/—	—	W	No
65	Parsons-Smith, B T	M	24	144/100	—	W	No
66	Pezzi, C , and Agostoni, G	M	41	175/125	—	W	No
67	Pezzi, C , and Agostoni, G	M	69	150/70	—	W	No
68	Potain and Bureau	M	40	220-230/—	—	W	No
69	Purks, W K, and Robert, W P	F	23	150/105	Unobtainable	W	No
70	Read, W T, Jr , and Krumbhaar, E B	M	35	over 200	—	C	Yes
71	Rosler, H	M	45	180/102	80/—	W	Yes
72	Routier, D , and Heim de Balzac, R	F	24	140/80	None in legs	W	No
73	Santas, M A	M	61	165/—	—	W	No
74	Schleckat, O	M	44	180/50	—	W	No
75	Shapiro, M J	M	6	134/80	Unobtainable	W	No
76	Starling, H J	M	40	255/148	—	W	No
77	Steiner, R	M	20	150-170/—	—	W	No
78	Strong, G F	M	18	140/90 (sick with low fever)	—	W	Yes
79	Strong, G F	M	38	220/90	—	W	Yes
80	Strong G F	F	12	160/80	—	W	Yes

TABLE II—*Continued*

No	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
81	Taylor, E F	F	33	190/60	could not be estimated	W	No
82	Taylor, E F	M	21	R 198/90 Later 168/82 and 154/64	Not possible to estimate pressure in fem arteries	W	No
83	Taylor, E F	F	59	175/110 A few days later 180/120	Not taken	W	No
84	Van den Berg, Heynsius	F	29	250+	—	W	No
85	Walker, W G	M father	48	R 158/82	L 108/94	W	No
86	Walker, W G	M son	18	R 166/108	L 130/116	W	No
87	Werlev, G	M	35	150/90	Slight oscill bet 110 and 100 (thigh) Tyco's	W	No
88	Wilson, M G	F	20	<u>180-220</u> <u>110-130</u>	120/- (femorals)	C	No
89	Woltman, H W and Shelden, W D	F	44	150/84	Lower thigh 100/-	W	No
90	Zenoni, C	M	66	205-220/-	—	W	No

these reports to identify the arm from which pressure readings were taken. There are six cases without autopsies in which the pressure was noted from an unspecified arm. If such readings were taken from the left arm, a hypertension in the right might have been overlooked. Lewis⁷⁷ points out that heart failure might bring about a fall of previously elevated pressure to within normal limits in some cases. In 15 of the 19 cases in this group there seems to have been either circulatory embarrassment, or gross failure, or chronic sepsis, sufficient to have reduced a previously elevated blood pressure to normal. Blackford's⁹ patient (case 3) complained of respiratory distress, including orthopnea, but developed neither cyanosis nor edema. The patient reported by Canculescu and Missirliu¹⁴ (case 5) was a boy of 14 years, who had had a protracted illness and who came under observation with signs of serious infection, cyanosis and circulatory insufficiency.

Hein⁴¹ seems to have reported a case of coarctation in which the circulation was compensated and in which a normal arm pressure was found. His patient complained of some dyspnea and cardiac pain but the circulation

CASES OF COARCTATION OF THE AORTA FROM 1892 TO 1936, WITH BLOOD PRESSURE READINGS

TABLE III

Blood Pressure of Arms Less than 140 (S)

No	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
1	Anderson, R G , quoted by Parkes-Weber and Knop	M	44	112/60	—	W	Yes
2	Bahn, K	M	40	115/75	—	W	No
3	Blackford, L M	M	24	R 128/88 L 122/90 ₁	—	W	No
4	Bode, O B and Knop, F	M	54	120/70	—	W	Yes
5	Canciulescu, M and Missirlu, V	M	14	115/85	85?	W	No
6	Focken, E	F	18	R 115/- L 105/-	—	W	No
7	Fray, W W	M	57	122/86	—	W	Yes
8	Hein, G E	M	32	122/80	—	W	No
9	Hein, G E	M	60	120/85	—	W	No
10	Hinrichsmeyer, C	M	32	<u>130-110</u> 95-85	—	W	No
11	King, J T , Jr	F	25	R 138/90 L 120-125/80	90/80	W	No unpublished
12	Kurtz, C M , Sprague, H B and White, P D	F	14	90/65	—	W	Yes
13	Kuschelewski, B P , Glikin, M I and Sysslin, D M	M	40	<u>115-105</u> 60-50	Not taken	W	Yes
14	Parkes-Weber, F and Knop, F	M	54	125/70	—	W	No
15	Pereiras, R , Inclan, R and Perez de los Reyes, R	M	7	105/-	—	W	Yes
16	Smith, F M and Hansmann, G	M	17	120/60	—	W	Yes
17	Stewart, H L and Bellet, S	M	26	R <u>126-136</u> 60	Not taken	W	Yes
18	Strassner, H	M	36	130/- R Rad	—	W	Yes
19	Umber	M	22	R 101/97 L 95/92	—	W	No

seems to have been fairly adequate Unfortunately in this case (number 8) no note was recorded as to which arm was used for the pressure determination

CASES OF COARCTATION OF THE AORTA FROM 1892 TO 1936, WITH BLOOD PRESSURE READINGS

TABLE IV

Mixed Blood Pressure Readings High in One Arm and Low in the Other

No	Author	Sex	Age	Blood Pressure		Color	Autopsy
				Arm	Leg		
1	Amberg, S	M	16	172/- and 108/-	100 and 94 (thigh)	W	No
2	Amberg, S	M	13	170/- and 90/-	Could not be recorded by usual means	W	No
3	Blackford, L M	F	44	R 164/86 L 126/110	R femoral 90/80	W	No
4	Deneke, T	M	46	R 185-220 85-90 L 106-120(?)	—	W	No
5	East, T	M	55	R 135/100 L 195/145	140/105	W	No
6	Hesdorffer, M B	M	23	R 178-210 90-110 L 108-120 92-90	—	W	No
7	Ratschow, M and Arendt, J	?	?	R 155/75 L 95/60	90/85	W	No
8	Turkington, S I	M	23	R 210/10 L 130/80	110/-	W	No
9	Villafañe, A P and Menendez, E B	M	20	R 215/115 L 115/-	—	W	No
10	Woltman, H W and Shelden, W D	M	20	R 164/86 I 126/110	A few slight oscillations bet 80 and 90	W	No

Hence, there is no well defined case so far recorded in which the circulatory compensation was above suspicion and in which the pressure in both arms was found to be normal

UNREPORTED CASES

Case 1 A young white woman of 18 years was seen at the Union Memorial Hospital through the kindness of Drs. Garis and Conley. She was admitted at the hospital for a lower right quadrant pain.

Past history was essentially negative, though some mild attacks of palpitation following exercise had been experienced over the previous six months. *The physical examination* showed a rather marked exaggeration of all pulsations in the upper extremities, especially that of the innominate. There was also a well marked pulsation in the second right interspace at the sternum, thought to be due to the mammary artery. Pulsations were felt in both interscapular regions near the scapulae at the level of the spines. A pulsating vessel of the size of one's finger was felt on each side. On the left, it was about three inches in length. On the right, while definite, it was less marked. There was a rough systolic murmur in both interscapular regions,

being loudest near the first dorsal spine *Heart* The P M I was exaggerated. Presystolic gallop was heard and a soft apical systolic murmur. Cardiac dullness was a trifle full to the left, measuring 9.5 cm to the left of the midline, 4 cm to the right. *Pulse* was bounding and of good volume at the wrists, but the abdominal aorta gave no appreciable pulsation. No pulse was felt over the femoral, dorsalis pedis or posterior tibial arteries. *The blood pressure* in the left arm was 195 systolic and 130 diastolic and in the right 180 systolic and 106 diastolic. No definite determination could be made in the legs and oscillations of the blood pressure needle were almost negligible. *The electrocardiogram* Rate 110. Rhythm regular. Conduction intervals P-R 0.18 second. Left axis deviation. T-waves upright in Lead I, biphasic in II, inverted in III. The laboratory findings were as follows:

Urine Sp gr 1.018. Appearance yellow and cloudy. Acid reaction. No albumin or sugar. There were no red cells, white cells or casts, but a large number of epithelial cells were seen.

The red cell count was 4,620,000, hemoglobin 102 per cent (Sahli). The white cell count was 13,500 with 81 per cent P M N and 19 per cent lymphocytes. The stained smear showed normal red cells and platelets. One c.c. of phenolphthalein intravenously yielded 70 per cent the first hour and 5 per cent the second hour. Non-protein nitrogen was 29 mg per 100 c.c., and fasting blood sugar 140 mg per 100 c.c.

Teleroentgenogram showed erosion of the inferior margin of the posterior part of most of the ribs, with slight cardiac enlargement to the left.

Case 2 A white woman, married, aged 24, was seen at the Hospital for the Women of Maryland through the kindness of Dr. Henry M. Thomas, Jr., who had made the diagnosis of coarctation of the aorta. The patient was a primipara, admitted to the obstetrical department in May 1934 when about four months pregnant. The family history was entirely unimportant. The past history revealed that the patient had been short of breath since childhood and had noticed an occasional sense of fluttering and some pain in the precordial area. She was not permitted to take part in athletics or gymnastic work at school by a physician's order. She was first examined in 1929 and was told that she had hypertension. Examination at the time she was three months pregnant showed blood pressure 200 systolic and 100 diastolic. The urine was clear. One month before delivery, non-protein nitrogen of the blood was 24 mg per cent. In November 1934, the patient entered the hospital and after the first stage of labor, lasting 11 hours, was delivered readily by low forceps (Scanlon maneuver). The baby, a normal male, was in good condition. The puerperium was non-febrile and uncomplicated. The post partum examination showed blood pressure 160-210 systolic, 90-110 diastolic in the arm, in the legs it was 110-140 systolic, 70-80 diastolic. Dr. Thomas discovered bilateral pulsations in the back just medial to the vertebral borders of both scapulae. There was the usual systolic murmur best heard in the interscapular region.

Laboratory tests were as follows:

Urine examinations were consistently negative for sugar and albumin.

Mosenthal test showed concentration power of 0.007.

Phthalein test showed an appearance time of 5 minutes with half hour excretion of 50, 15, 10 and 5 per cents for a two hour total of 80 per cent.

Blood Wassermann was negative.

Blood chemistry on 6/19/34: non-protein nitrogen 26 mg per cent. Uric acid 24 mg per cent. Creatinine 1.3 mg per cent. A repetition showed on 10/16/34: non-protein nitrogen 24 mg per cent, uric acid 2.6 mg per cent, CO_2 combining power 61 volumes per cent. *Teleroentgenogram*: Notching of the inferior rib margins. Cardiac shadow within normal limits. Defect in region of aortic knuckle in both antero-posterior and oblique views.

Remarks: This patient was carefully observed during pregnancy, but was thought

to be suffering from malignant hypertension. While she was delivered without complications, she was advised to avoid further pregnancies.

Case 3 A white, single woman of 22. She was a patient at the Johns Hopkins Hospital in July 1932, complaining of high blood pressure, kidney trouble and burning on urination. Family history contained nothing of relevance. The patient had been subject to frequent headaches with dizziness. She had nocturia two or three times. The urine was quite normal. The gynecological examination was normal. The physical examination was as follows:

There was a distinct difference in the degree of pulsation in the arms as compared with the legs. The abdominal aorta was barely felt and pulsation in the femorals and dorsalis pedis was not made out. There was no history of nocturia prior to one year ago, no intermittent claudication, but she had suffered from numbness and coldness of legs requiring her to get out of bed and use or rub the legs. On careful palpation very slight left dorsalis pedis pulsation was felt. There was mottled cyanosis of the lower legs. P M I was vigorous when patient was supine. There were no shocks or thrills. Dullness was about 4 by 7½ cm. No increased retromanubrial dullness. Sounds vigorous at apex with soft systolic blow, practically absent in erect posture. Accentuation of A₂ and P₂. Systolic murmur of moderate intensity heard over root of the aorta, no diastolic, very large pulsation in episternal notch. Bilateral pulsating vessels about the size of small finger just at the inner margin of each scapula running roughly up and down. No appreciable murmur on the right side, short rough systolic murmur in left interscapular region, at about the level of the spine. Arteries of fundi very tortuous and there was definite slight pulsation of the arterial trunks. Vessels were more numerous than normal.

Teleoecentgenogram Typical rib erosions. "Chimney" shaped aortic shadow. No cardiac enlargement.

Further examination revealed chronic tonsillitis and enlarged adenoids. Basal metabolic rate was between +15 and +23 per cent, without definite signs of hyperthyroidism. Blood pressure arms 180 systolic and 102 diastolic, legs 110 systolic, and diastolic not known.

The electrocardiogram was normal. T₁ was inverted. Blood chemistry non-protein nitrogen 31 mg per cent. Phenolsulphonephthalein elimination was 65 per cent for 2 hours. Urinary concentration test showed a variation of specific gravity from 1.002 to 1.026. Only 130 cc of urine were passed between 7 p.m. and 7 a.m. as against 1825 during the preceding day. Blood Wassermann reaction negative.

Diagnosis Isthmus stenosis.

Case 4 A 15 year old white boy, seen by courtesy of Dr T B Fletcher. There was no complaint. Family history was negative. Past history tonsillectomy at two years of age. Present illness. Patient has no symptoms under ordinary circumstances. Specifically, there is no dyspnea on ordinary exertion. When running, he is conscious of shortness of breath but there is no palpitation or precordial distress. There is no edema and no nocturia.

The physical examination was negative except as noted below. The retinal arteries were distinctly tortuous but showed no A-V compression and there were no hemorrhages or exudates. There was no cardiac shock or thrill. Pulsation of dorsal scapular arteries was well felt in both interscapular areas. The radial pulses were full, bounding—the right apparently of higher tension and fuller volume than the left. No pulsation was felt in the abdominal aorta, femoral or popliteal arteries. Pulsation could barely be felt in the posterior tibial and dorsalis pedis arteries. The blood pressure in the right arm was 174 systolic and 94 diastolic, in the left arm 142 systolic and 90 diastolic, in both legs about 100 systolic and 70 diastolic. Pulse was regular, not accelerated. At the apex was heard a soft systolic murmur which disappeared on exercise. Over the base a harsh systolic murmur was heard which was trans-

mitted upward and outward on both sides. It was heard best in the two interscapular areas.

The Wassermann reaction was negative. Blood non-protein nitrogen 43 mg per cent. Red blood cells 5,020,000, hemoglobin 15.4 gm, white blood cells 5,500. Phenolsulphonephthalein kidney function test showed 75 per cent elimination in 2 hours. The urine was normal.

It is of some interest that the erosion of the under surfaces of the ribs is already apparent in the roentgenogram of this patient. The cardiovascular stripe is also of

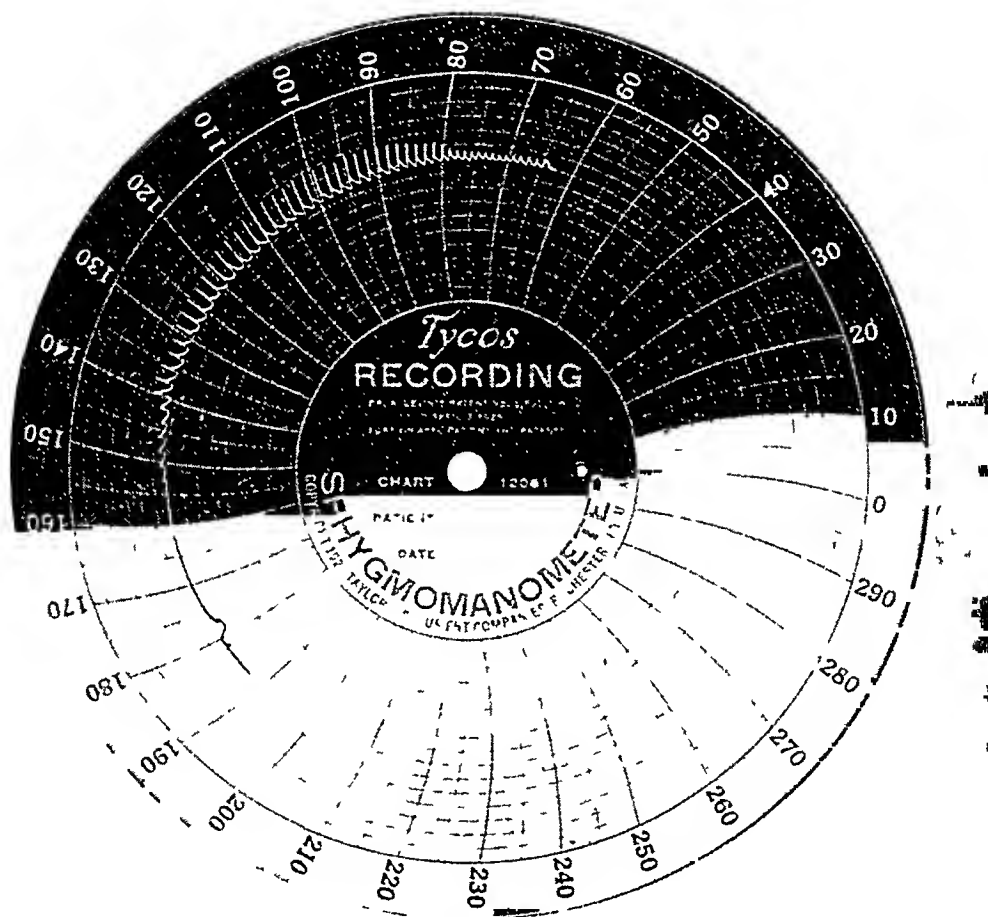


FIG 1 Record of blood pressure from right arm in case 5. Systolic level is about 138, diastolic, about 80.

typical contour. Unfortunately, there are no previous roentgenograms to indicate the age at which rib erosions became apparent. The heart was not enlarged.

Case 5. A white matron, aged 25, of Jewish extraction, consulted me in January 1929. The family history was not relevant. She had had one healthy child, no miscarriages. A second healthy child was born in 1930. There was no complication with either pregnancy.

The single persistent symptom was excruciating headache, which had tormented the patient as far back as she could remember. My impression on seeing her in 1929

was that the headaches were probably associated with the isthmus stenosis of the aorta, possibly due to actual aneurysm of the cerebral vessels. However, there was no severe headache from the time of her second pregnancy until I saw her in 1932.

The immediate symptom for which this patient consulted me was cardiac palpitation, of extrasystolic type.

The examination follows. The patient looks well but somewhat lean. Color good. Very slight increase in pulsations in the neck. Axillaries are visible but not the ulnar vessels. Eyes. Pupillary reactions normal. Transient lid-lag. Nose. Nor-

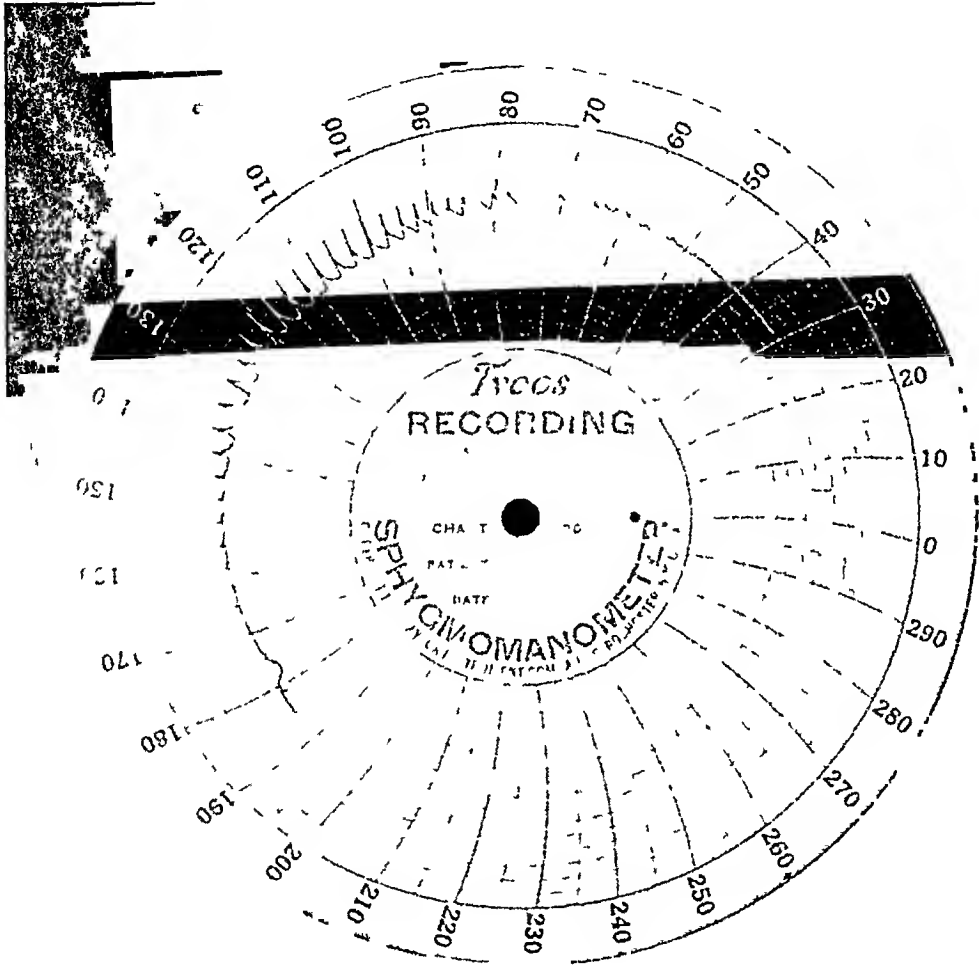


FIG 2 Blood pressure from left arm in case 5. Pressure about 123/87

mal. Mouth and throat. Quite normal. Tonsils small. Glands. Cervicals not enlarged. Thyroid. Normal. Chest. Resonant. Breath sounds normal. No retro-manubrial pulsation and no significant dullness. Back. There is a definite pulsation along the inner margin of the left scapula, but I find it difficult to outline the shape of the vessel. A similar vessel is felt in the right interscapular region. They feel like the usual collateral vessels in such cases but are smaller. There are no other collateral arteries to be felt over the back. There is a moderately intense systolic murmur in each interscapular region. A systolic murmur is heard over the entire

back of the chest to within 3 fingers-breadth of the right base and all the way to the left base. It is a little louder in the left interscapular region than anywhere else. Breath sounds everywhere normal. No râles.

Heart P M I is made out in the fourth space, in the natural position. No shock or thrill. Rather marked pulsation in the region of the pulmonary conus. Cardiac dullness right 3.5 cm, left 8.5 cm. Sounds at apex perfectly normal. There is a barely audible systolic blow. At the base both second sounds are slightly increased. There is a grating systolic murmur over the pulmonic area referred to the left clavicle.

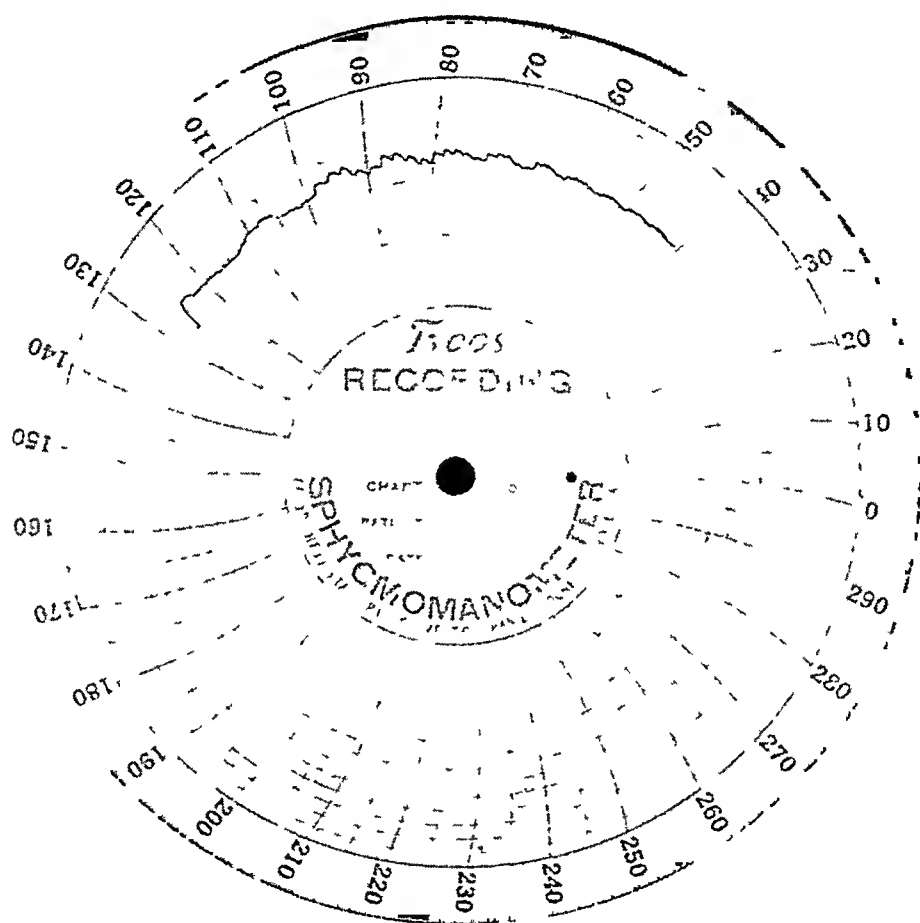


FIG 3 Showing extreme reduction of pulsation in leg, with systolic blood pressure less than 100. Case 5

Abdomen On deep palpation a slight but definite pulsation is made out in the abdominal aorta. There is also a slight pulse to be felt in the right femoral artery but this is much reduced from normal. A similar pulsation on the left. Cecum is palpable. Liver not made out, neither is the spleen.

I can feel no pulsation in the left dorsalis pedis, nor in the right. There is a very slight pulse in the right posterior tibial and in the left.

Pulse At the wrist is big, regular. Rate 84.

Blood pressure Right arm 122 systolic and 66 diastolic at 2 30 p m (two hours after lunch which included tea Smoked a few cigarettes after lunch) Left arm 128 systolic and 66 diastolic

Blood pressure 1/30/29 Right arm 122 systolic and 60 diastolic Left arm 120 systolic and 60 diastolic

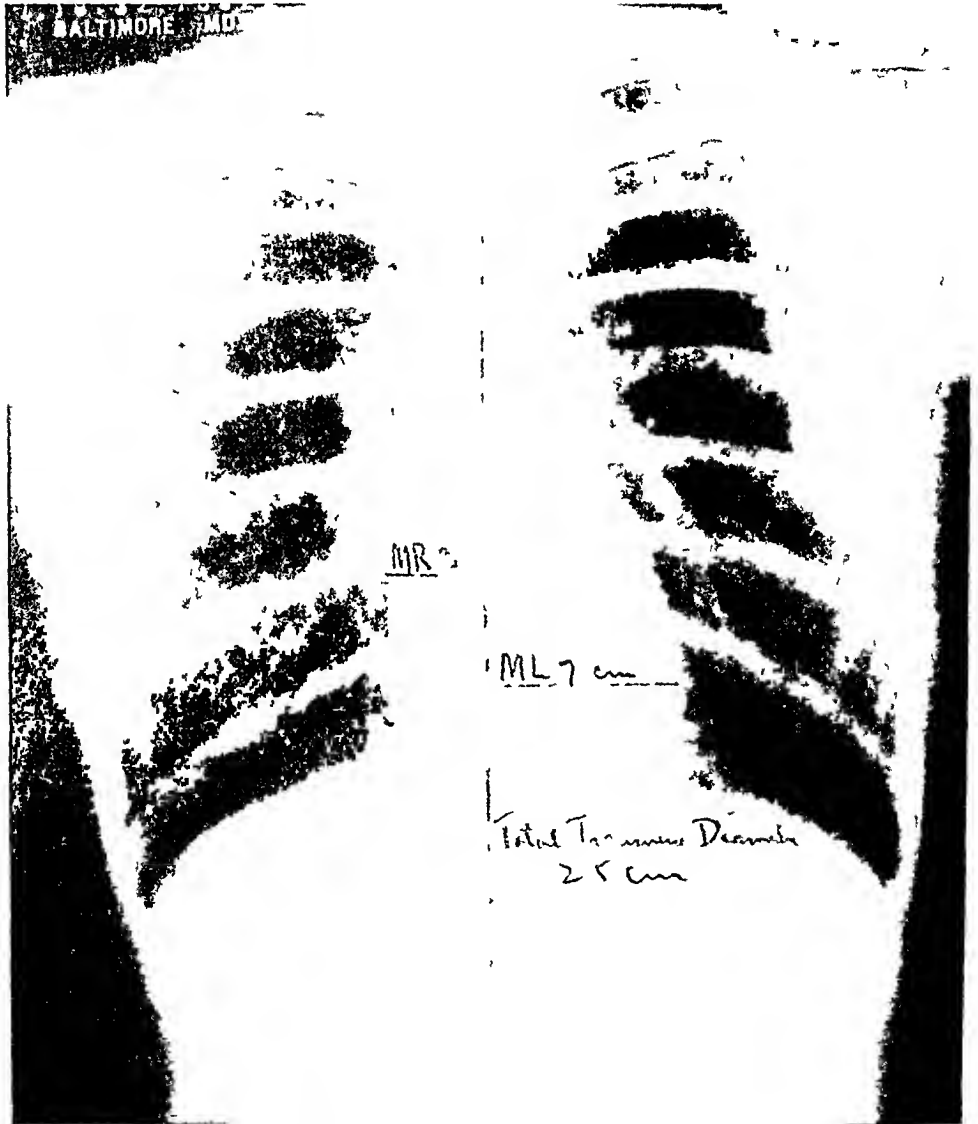


FIG 4 Film from case 5, showing characteristic tubular aortic shadow Somewhat deficient at the knuckle without rib erosion

Right popliteal 104 systolic and 90 diastolic Left popliteal 108 systolic and 90 diastolic (See figures 1, 2, 3)

Electrocardiogram Rate 100 Rhythm regular P-waves upright and slightly notched in Leads I and II, especially in II, diphasic in III R-waves of normal sequence P-R 0.15 sec Q-R-S 0.06 sec S-T normal T-waves upright, normal
Diagnosis normal tracing

Dr. C. A. Waters' Roentgen-Ray Report "The roentgen-ray examination of the chest fails to show any erosion of the under surfaces of the ribs due to pressure from hypertrophy of the intercostal arteries. The ascending arch of the aorta looks to be a little enlarged and there is also some prominence of the innominate artery. The descending arch is not at all prominent and the heart is unusually small, the transverse diameter measuring only 10 cm divided as follows: M. R. 3 cm, M. L. 7 cm. The transverse diameter of the chest is 25 cm. There are numerous calcified glands noted, chiefly on the left side. There is no parenchymal infiltration. The apices are essentially clear. There is certainly nothing in the roentgen-ray examination to indicate coarctation of the aorta." (See figure 4.)

Diagnosis 1 Isthmus stenosis (coarctation) of the aorta

2 Extrasystolic arrhythmia

Comment The recordings of the blood pressure showed a systolic level in the right arm of about 138, with a diastolic level about 80, in the left arm the recorded pressure was 123 systolic and 87 diastolic. In the leg, the oscillations were minute and occurred between 90 and 100 mm. There was definite evidence of collateral arterial circulation in the interscapular region and a well marked systolic murmur, maximum in the left interscapular region. These findings seem to establish the diagnosis of isthmus stenosis beyond reasonable doubt, however, the relative normality of the arm pressure and the lack of rib erosions suggest that the degree of narrowing is not great. This is the only case of coarctation I have seen in which the arm pressure was within normal limits.

DISCUSSION AND CONCLUSIONS

It is clear from the tables that hypertension in the arms is the rule in cases of coarctation of the aorta. The pressure in the right arm is usually higher than that in the left and there is a group of nine cases in which this difference was so marked that the systolic pressure in the left arm was within normal limits. At the same time, it is not unusual to find a diastolic hypertension in the left arm in the face of a normal systolic level.

Mention should be made here of the numerous observations of asymmetric blood pressure in the two arms that have been noted in apparently normal individuals. For example, Korns and Guinand,⁴⁸ taking 10 mm Hg as the upper limit of normal discrepancy, found asymmetry of the brachial pressure in 22 per cent of apparently normal subjects. In this group with discrepancy in the two arms, the higher pressure existed in the right arm in three-fourths of the cases. Stieglitz and Propst⁹³ have recorded similar findings. In their cases 15.7 per cent showed asymmetric brachial pressure readings, the higher pressure in the majority of cases being found in the right arm. Various postulates, such as cervical rib, aortitis, arteriolar spasm, injury, arterio-venous aneurysm and central trophic disorders are suggested as possible causes of such discrepancy.

However, the second report shows that asymmetric readings of pressure are most to be expected at the extremes of pressure, either high or low, and that the discrepancy tends to disappear as the pressures approach normal. This observation, together with the high incidence of asymmetry reported by Korns and Guinand⁴⁸ in supposedly normal persons, suggests that such differences in the two arms are probably common among normal subjects,

especially when the pressure is determined only once. Doubtless, some of the discrepancies can be attributed to organic bases, such as cervical rib.

These findings tend to minimize the significance of such differences in brachial pressure as are recorded in table 1. It is true, however, that the inequality is rather more constant and striking among the cases of coarctation than might be expected in cases of generalized hypertension, though there can be no certainty of this until a large number of observations on the brachial pressures of hypertensive subjects becomes available. At any rate, it becomes clear that many of the discrepancies of pressure in table 1 are probably within normal limits.

Table 4 is more difficult to explain on the basis of normal variation. Korns and Guinand⁴⁸ reported a maximal difference of 38 mm Hg and an average of 14.3 mm in their group with asymmetric pressures. It is possible, even likely, that an organic basis existed to explain some of these discrepancies. The differences of pressure in table 4 are beyond the maximal systolic difference noted by Korns and Guinand⁴⁸ in all but one case, and in that case it was exactly 38 mm.

For these reasons, the presence of hypertension cannot be relied upon as a certain index to isthmus stenosis. If the pressure is taken in the left arm, a normal pressure might be found even in the presence of a marked hypertension in the right arm. Cases that have progressed to a state of cardiac failure or cases in which there has been a chronic infection or other debilitating disorder, may show a pressure in both arms that has fallen from an abnormally high level to within normal limits.

Case 5 in the present series also indicates that erosion of the ribs is not necessarily present in a typical coarctation. It is known that rib erosions may not be present in childhood, but in case 5 the patient was an adult. It is my belief that the demonstration of collateral arterial circulation is the most important single clue to the diagnosis of coarctation. It has been present in each of some 16 cases I have seen. Moreover, the incorporation of a search for collateral arterial pulsation in the interscapular region into a routine physical examination is readily achieved. The finding of typical murmurs in the back is also in my opinion a more important single clue than the level of blood pressure in the arm.

Finally, mention should be made of the fact that Lewis⁵⁷ emphasized the regularity with which hypertension could be expected in the adult variety of coarctation, provided the slighter degrees of narrowing were excepted together with those cases in which cardiac failure or protracted illness might have lowered a previously elevated pressure to within normal limits. In case 5 of this present series there is reason to believe that the degree of stenosis is not great, though a typical collateral circulation was found, together with a striking difference in the degree of pulsation and in the pressures of arms and legs. We have no way of determining whether the stenosis in this case is of the infant or adult type. The fact remains, how-

ever, that coarctation sufficient to produce characteristic physical signs and asymmetry of pressure between arms and legs may exist in an adult together with normal arm blood pressure

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MASSIVE ATELECTATIC COLLAPSE OF THE LUNG COMPLICATING PNEUMOCOCCUS PNEUMONIA¹

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MASSIVE atelectatic collapse of one or more lobes of the lung, occurring during the course of primary lobar pneumonia or complicating recovery from this disease, has been recognized by very few writers. In most articles dealing with pneumonia, either this complication is not mentioned at all or it is merely dismissed as a possible but exceedingly rare complication. Several reports of its occurrence in the pneumonias of infants and children have appeared during the past few years¹⁻¹⁰ but very few instances have been recorded in cases of acute lobar pneumonia in adults,¹¹⁻³¹ although it was recognized as far back as 1881, or even earlier.¹¹

The characteristic findings of massive atelectasis involving one lobe or one lung have been recognized in the roentgenograms in 62 cases of primary pneumococcus lobar pneumonia in adults at the Boston City Hospital in the past seven years. During the same period, varying degrees of atelectasis were noted in the lungs at necropsy in 47 cases of pneumococcus pneumonia of various kinds. A number of the cases exhibited striking clinical features. It is of interest, therefore, to present briefly some illustrative cases and to review separately some of the features of the cases recognized by roentgen-ray and of those noted at autopsy.

CASES REPORTED IN THE LITERATURE

The early history of pulmonary atelectasis in relation to pneumonia is recorded in the studies of Rommelaere.¹¹ According to this writer, Laennec encountered this condition in pneumonia with effusion, and Grisolle and Traube used the words "splenisation" and "carnification" which they considered to represent different types of inflammation. Rommelaere described most of the physical signs and anatomical findings in atelectasis occurring during pneumonia and emphasized the presence of mucoid sputum and the lack of displacement of the cardiac impulse in differentiating this condition from pleural fluid. He also noted that bronchophony and bronchial breathing may be present in some cases while in others the breath sounds may be entirely absent. He believed that the collapse occurred only outside the

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inflamed portion of the lung and that the sudden appearance of this collapse may be the cause of death in some cases. He described two such cases, one was diagnosed by the failure to obtain fluid by thoracentesis and the second, which occurred during an otherwise uneventful convalescence three weeks after the onset of typical lobar pneumonia, was diagnosed by physical signs and confirmed at autopsy.

Recent interest in massive collapse of the lung dates from two important groups of observations made by Wm. Pasteur, the first relating to collapse of the lower lobes occurring in cases of diphtheria and ascribed to paralysis of the diaphragm³² and the other to a similar condition occurring after abdominal operations and considered by him to be due to reflex inhibition of diaphragmatic movement³³. The condition has since been frequently recognized and described as a complication in a variety of conditions including (1) surgical operations, (2) trauma to the chest or elsewhere, (3) after hemoptysis in pulmonary tuberculosis, (4) in cases of bronchiectasis, (5) obstruction of bronchi due to foreign bodies or tumors, or (6) from pressure outside the bronchus, and (7) in nervous and debilitated individuals with pulmonary hypoventilation. An extensive bibliography is included in a recent paper by Bowen³⁴. Inasmuch as the primary interest in the present paper concerns atelectasis as a complication of pneumonia, only the literature pertaining directly to this subject will be cited.

As previously noted, massive atelectasis indicated by a shift of the mediastinal contents to the affected side, has been encountered more often in the pneumonias of infants and children. Thoenes¹ reported 11 cases in which this condition was definitely demonstrated in the roentgenograms. Most of his children were undernourished and had atypical pneumonias, but cases of typical unilateral lobar pneumonia in previously healthy children were also included. One or more lobes of the right lung were affected in 10 of his 11 cases, the upper lobe being most frequently involved. There were autopsies in four of these cases. In two the heart had returned to a normal position, in one there was partial atelectasis and in the fourth massive collapse with the mediastinum pulled over to the affected side. Wallgren² reported eight cases in children ranging in age from six months to nine years. The involvement was right-sided in three and left-sided in five, and probably began during acute pneumonia. Some of his cases may have had the atelectasis at the time of the onset of the pneumonia. All had cleared after intervals varying from a few weeks to a year. Griffith³ criticized the observations of the last two authors mainly on technical grounds. However, in careful roentgen studies in 40 cases of pneumonia in young children, he noted definite and sometimes marked displacement of the heart to the affected side with subsequent return to normal position in 16 cases with unilateral involvement, but did not make sufficient observations to determine when this condition began or how long it lasted. Although admitting that atelectatic patches in the consolidated lung might aid the displacement, this writer ascribed the condition to overdistention of the unaffected lung. Tal-

lerman and Jupe⁴ described a similar occurrence in five children, including three with lobar pneumonia and two with bronchopneumonia, in all of whom the condition cleared completely. In one of their cases there was pneumonia with atelectasis on the right side which cleared at the time when the left lung became involved with pneumonia but without atelectasis. They considered the cardiac displacement due to both the partial collapse of the affected lung and the push of the sound overdistended lung. Findlay⁵ reported the case of a child of seven who, when first seen one, possibly two weeks after the onset of a pneumonia, was afebrile but had much mucopurulent sputum. Partial collapse of the left lower lobe was noted by physical and roentgen examination. He noted bronchial breathing and increased spoken voice at some examinations and absent breath sounds at others. The condition cleared completely in 2½ weeks after a roentgen-ray examination with lipiodal, followed by carbon dioxide inhalations. Gleich⁶ reported a case of lobar pneumonia of the right lung in a child with complete situs transversus in whom the physical signs alternated between those of atelectasis and those of consolidation for six weeks. Ellis⁷ reported eight cases of atelectatic bronchiectasis in children. In five of his cases there was a typical history of pneumonia in which the symptoms persisted for an unusually long time and bronchiectasis with atelectasis was present when they were first seen five or more years later. A sixth case had a typical right lower lobe pneumonia with fever for 16 days. On the thirty-third day collapse of the right lower lobe was diagnosed by roentgen-ray on the basis of a dense triangular shadow in the cardio-hepatic angle. This cleared up completely with breathing exercises in two months, and no bronchiectasis developed. Nordgren⁸ reported the case of a girl of 14 years, with a long asthmatic history, in whom massive atelectasis with induration and scoliosis developed in the right lower lobe one month after the onset of typical lobar pneumonia in this lobe, and in whom the lungs were entirely clear one month later. He ascribed the atelectasis to occlusion of bronchi with pneumonic exudate. Anspach⁹ studied 50 cases presenting, by roentgen-ray, a triangular shadow at the base of the lung in the cardio-hepatic angle, both with and without bronchiectasis. Some of these cases had bronchopneumonia without foreign bodies in the bronchi at autopsy. Some later developed bronchiectasis, while others cleared without developing bronchiectasis. The commonest history was that of an acute pulmonary process with physical signs of lobar pneumonia followed by decreased breath sounds. In 41 cases there was pneumonia with collapse. He ascribed the collapse to obstruction by pneumonic exudate, the bronchiectasis developing if the atelectasis persists. Blanton and Morgan¹⁰ reported the sudden onset of massive atelectasis of the right lung in a five weeks old infant on the ninth day after the onset of a pneumonia of the right lower lobe and three days after the fever had subsided. This infant had paroxysms of cough followed by vomiting, the vomitus containing sticky

mucus Within a week there was patchy aeration of the lung and the heart returned to normal position after one month

Fewer instances of this complication have been noted in the pneumonias of adults Gwynn¹² reported two cases in elderly patients with typical lobar pneumonia of the right lower lobe, who had a sudden episode of extreme dyspnea lasting several hours, after which massive collapse of the right lung with the heart markedly displaced to that side was demonstrated clinically In the first patient the collapse occurred on the nineteenth day of illness during an otherwise uncomplicated convalescence with resolution, and in the second it occurred on the fourth day of an acute illness during which there was much mucoid sputum A third patient, who had bronchitis or bronchopneumonia of the left lower lobe, also had a similar episode with collapse of the entire left lung In each of these cases, the heart returned to normal position in five to seven days Peppard¹³ reported four cases in which collapse occurred in the right lung 10, 8, 6, and 2 days, respectively, after the onset of pneumonia, the lungs previously being noted as having pneumonia without collapse In three of these cases there was typical lobar pneumonia and the left side was later involved without evidence of atelectasis The fourth patient was described as having bronchopneumonia and the collapse cleared in three days, whereas in the other three cases it cleared more slowly Jacobaeus¹⁴ reported a case of lobar pneumonia of the right upper lobe in which collapse suddenly occurred on the eighteenth day and gradually cleared within six months The location of the lesion and the delay in clearing suggested pulmonary tuberculosis but this was ruled out by repeated negative sputum examination and by the subsequent course A second patient had central pneumonia and developed collapse of the right lower lobe Jacobaeus¹⁵ also reported a case of acute bronchitis with scattered râles, but more on the left side On the third day of illness this patient had an attack of dyspnea which was found to be associated with massive collapse of the left lung and a shift of the mediastinal contents to that side The condition had cleared completely three weeks later Mohler¹⁶ reported two cases The first had marked dyspnea following a vomiting spell, and collapse of the right lung was demonstrated six hours later The patient had slight fever but no leukocytosis and cleared rapidly and completely The second case had typical pneumonia of the right upper and middle lobes and auricular fibrillation The pneumonia was apparently clearing on the sixth day but the patient was raising thick tenacious sputum On the ninth day there was evidence of collapse of these lobes by physical examination and in the roentgenogram Corrylos and Birnbaum^{17, 18, 19} presented extensive experimental evidence and some clinical data to support their contention that lobar pneumonia is merely a lobar atelectasis with infection They advocated bronchoscopic aspirations, while Henderson²⁰ advocated carbon dioxide inhalations for treatment early in the disease Manzer²¹ reported two cases in which typical collapse of the lung was

rapidly relieved by bronchoscopic aspiration of gelatinous material. The condition was ushered in with chill and fever, in each case. Wu²² and Graeser, Wu and Robertson²³ reported a careful study of the roentgenographic findings and physical signs in 40 cases of lobar pneumonia in adults. Elevated diaphragm on the affected side was noted in 18 cases. In four cases they observed a definite shift of the mediastinal contents to the affected side during resolution. This was especially marked in one case in which it lasted at least 29 days but the lungs had returned to normal in two months. There were three other cases with slight but definite atelectasis during the acute disease, and they have observed another more striking case outside the series in which the collapse was noted on the second day of illness. Two of the cases died three to four days after the last observation, and the mediastinal contents were found at autopsy to be in normal position. Hart²⁴ noted that displacement of the heart, trachea, and diaphragm to the affected side is common in pneumonia. Korol²⁵ suggested roentgenograms in suitable positions to differentiate empyema from large areas of atelectasis in cases with prolonged signs and symptoms. Rigler²⁶ presented the roentgenograms of a rare case, in which the entire right lung was dense but the mediastinum was in normal position on the fifth day, but in which after an acute attack of dyspnea and cyanosis 12 hours later, the heart and trachea were shown to be definitely displaced to the right, indicating a superimposed atelectasis. Sante²⁷ also mentions this complication as a rare occurrence during resolution with rapid absorption of pneumonic exudate without removal of the material obstructing the bronchi. Davidson and Freedman²⁸ reported a case of atelectasis and fibrosis of the left lower lobe which presumably began as a collapse complicating pneumonia 25 years previously, when the pulmonary symptoms began. Fletcher and Dimson²⁹ reported a case of pneumonia of the left lower lobe in which atelectasis was first demonstrated on the eleventh and again on the twenty-first day after the onset of pneumonia, but was shown to have cleared entirely four months later. Mayoral³⁰ included among his cases of "shrunk lung" two in which the condition was attributable to lobar pneumonia. One had an earlier history of pneumonia and presented atelectasis of the right lower lobe with the heart displaced to that side. Biopsy of the partly occluded bronchus showed only fibrosis. The other case had a prolonged convalescence from pneumonia of the right lung without atelectasis demonstrable in the first roentgenogram. A second roentgenogram 20 days later and a third, six weeks after that, showed fibrosis and unresolved pneumonia with atelectasis and the heart was displaced to the right. Butler³¹ reported a case of post-pneumonic empyema associated with atelectasis in which there was poor healing and failure of the cavity to close although there was no air in the pleural cavity. In the roentgenogram the underlying lung looked dense, suggesting carcinoma. Bronchoscopy showed stenosis of the major bronchus without foreign body, tumor, or exudate. Rapid improvement

followed this procedure and later no collapse could be demonstrated in the bronchus

CASES FROM THE BOSTON CITY HOSPITAL

Many cases of pneumonia have been encountered in which repeated examinations revealed physical signs over the affected lobes alternating between those suggestive of fluid and those indicative of frank consolidation. This has occurred during the acute illness or at various stages during an otherwise uneventful convalescence. In a number of such cases, evidence indicating varying degrees of atelectatic collapse of the lung may be obtained by carefully noting the position of the heart, trachea, and diaphragm at each of the examinations. The signs of atelectasis can not always be verified by the roentgenogram unless it is ascertained that the characteristic signs are present immediately before and after the film is taken and necessary precautions in technic are observed to avoid distortion and to maintain comparable perspective in successive films. When massive atelectasis involves an entire lobe—either one that was previously uninvolved, or a partially consolidated lobe, or one in which resolution has already progressed to the point where a good proportion of the exudate has been removed or absorbed from the alveoli—the physical and roentgen-ray signs are easy to discern provided that this condition is borne in mind.

In the present study, two groups of cases will be considered. The first group includes cases in which the clinical and roentgenographic evidence of frank lobar pneumonia was unmistakable and specific types of pneumococci³⁵ were obtained from the sputum or blood, or both. Cases following operations, parturition, and injuries were excluded. Inasmuch as the physical signs and even roentgen-ray findings of minor degrees of atelectasis in acutely ill patients are not always convincing unless special precautions and technics are employed,^{23, 36} only those cases in which obvious massive collapse of one or more lobes was observed in the roentgenograms were selected. Sixty-two cases observed between 1929 and 1936 are included in this group. Certain features of these cases are analyzed in table 1. The second group comprises 47 cases of pneumococcus pneumonia (both lobar and atypical) in which atelectasis of various degrees was made out at autopsy. In each instance, type-specific pneumococci were cultured from the consolidated lung and other sources at autopsy and, in almost every instance, the same type pneumococcus was obtained during life. Although one or more roentgenograms were made in most of these cases, atelectasis was not definitely diagnosed from these films. These two groups of cases will be considered briefly and abstracts of a few cases selected to illustrate certain clinical features will be presented. A considerable number of cases not included in these two groups exhibited roentgen-ray evidence of moderate to marked elevation of the diaphragm on the affected side without shift of the mediastinal contents. Since it is reasonable to assume that this con-

dition may result solely from reflex inhibition of diaphragmatic movement, these cases have been omitted although some may indeed represent cases of massive collapse

Cases Showing Massive Atelectasis in Roentgenograms (Table 1)
The collapse was first made out during the acute disease in 34 of the 62

TABLE I

Analysis of 62 Cases of Pneumococcus Lobar Pneumonia in Which Massive Atelectatic Collapse of the Lung Was Recognized in Roentgenograms

A Collapse First Seen during the Acute Disease				B Collapse First Seen during Resolution				
Day of First X-Ray Showing Collapse	Number of Cases	Previous X-Rays Without Collapse	Later X-Rays Without Collapse	Day of First X-Ray Showing Collapse	Number of Cases	Previous X-Rays Without Collapse	Later X-Rays Without Collapse	No Previous X-Rays Taken
1	2	—	—	7	1	0	1	1
2	3	—	2	8	3	0	3	3
3	5	—	3	10	4	3	1	1
4	2	—	1	11	4	4	2	0
5	6	—	2	12	1	0	0	1
6	5	1	1	14	3	3	1	0
7	4	1	3	15	3	3	2	0
8	3	1	1	16-21	4	3	2	1
9	4	—	2	22+	5	5	1	0
Total	34	3	15	Total	28	21	13	7

C Lobes Involved		D Age Groups		E Pneumococcus Types			
Lobes	Cases	Years	Cases	Type	Cases	Type	Cases
Right lower	20	12-19	1	I	23*	XI	1
Right upper	9	20-29	6	II	7†	XIII	1
Right lower and middle	6	30-39	21	III	3	XIV	1
Right lung	20	40-49	20	IV	2	XVII	1
Right lung	5	50-59	11	V	5	XVIII	1
Left lower	2	60-69	1	VII	5‡	XIX	1
Left lung		70+	2	VIII	9	Neg I-XX	2

* Including 9 serum treated

† Including 2 serum treated

‡ Including 2 serum treated

cases In three of these cases, previous films showed pneumonia without evidence of collapse, in the remaining cases the collapse was noted in the first film Later films showed the return of the mediastinal contents to normal position in 15 of these cases In most of the other cases no later

films were taken because of the favorable and apparently uncomplicated convalescence or because death ensued. One case showing atelectasis on the first day still showed the mediastinal contents deviated to the affected right side 12 days later.

Six of these 34 patients died, and autopsies done in four failed to show atelectasis. In one of these autopsied cases there was organizing pneumonia in the right lung. This lung had been shown by roentgen-ray to be collapsed 24 days before death, but not 16 days later. In the other three autopsied cases, death occurred on the fifth, eighth and ninth day of illness or four, five, and four days, respectively, after the atelectasis was demonstrated by roentgen-ray. Of the two patients who died and had no autopsy, one had a second roentgenogram showing the mediastinum in normal position and in the other the atelectasis was demonstrated on the day of death.

Fluid was demonstrated by thoracentesis in four of the surviving cases at the time when the mediastinum was deviated to the affected side. In two instances this fluid was sterile and resorbed spontaneously, and in the other two it was infected and required treatment by open thoracotomy and rib resection.

There were 28 cases in which the collapse was first made out in roentgenograms taken after the fever and acute symptoms of pneumonia had subsided. In 21 of these cases, previous roentgen-ray films showed the characteristic findings of lobar pneumonia but no evidence of mediastinal displacement. In the remaining seven cases no previous roentgen observations were available. Subsequent roentgen-ray films showed that the mediastinal contents had returned to their normal position in 13 cases before the patient left the hospital. In most of the remaining cases either the collapse was still present or no further observations were available during the patient's stay in the hospital. Observations were made in four patients for three to 27 months after they left the hospital. In all of these four patients, the mediastinal contents were displaced to the affected side at the time of discharge from the hospital but, in three of these cases, they had returned to normal position at the time of the last observation. The day of the disease when collapse was first noted, the lobes involved, the age of the patients, and the pneumococcus types in these cases are summarized in table 1.

*Cases of Pneumonia with Atelectasis at Autopsy** Some of the more relevant features of these cases are analyzed in table 2. The 47 cases of this group occurred among 684 cases of pneumococcus pneumonia in which autopsies were done at the Mallory Institute of Pathology of the Boston City Hospital during the seven years ending July 1936³⁷. As in the first group, cases occurring after operations, parturition, and injuries were omitted. No definite evidence of collapse was noted during life in any of these cases except in the two cases of bronchogenic carcinoma. It is ap-

*We are indebted to Dr. Frederick Parker, Jr., for permission to use the autopsy protocols.

TABLE II

Certain Features of 47 Cases of Pneumococcus Pneumonia in Which Pulmonary Atelectasis Was Found at Autopsy

	Number of Cases
A Probably congenital atelectasis	1
(a) Infant, aged 4 days, bronchopneumonia, Type XI	
B Atelectasis probably due to obstruction	4
(a) Carcinoma of bronchus, 2 cases of bronchopneumonia (Types I and VI)	
(b) Inhaled food and bronchopneumonia, 2 cases	
(1) Infant, aged 2 days, Type XIX	
(2) Perforated esophagus, age 30 years, Type VI	
C Atelectasis associated with compression from pleural fluid	13
(a) Types I, 5, V, 2, III, IV, XI, XII, XIII and XVIII, 1 each	
(b) Ages Newborn, 1, 12 to 29 yrs, 3, 40 to 49 yrs, 3, 50 to 59 yrs, 3, 60 to 69 yrs, 2, 70+ years, 1	
D Partial or scattered atelectatic collapse	13
(a) Bronchopneumonia, 4, Lobar pneumonia, 9	
(b) Resolution and organization in collapsed lobe, 6	
(c) Hypostatic (?)—involving postero-inferior portions, 4	
(d) Early pneumonia in the collapsed lobe—?extension, 2	
(e) Atelectasis only in consolidated lobes, 6, only in non-consolidated lung, 5, in consolidated and non consolidated lobes, 2	
(f) Types I, 1, II, 2, III, 1, IV, 2, V, 2, XII, 2, VIII, IX, XVIII, 1 each	
(g) Ages 2 mos, 1, 2 yrs, 1, 40 to 49 yrs, 4, 50 to 59 yrs, 5, 60 to 69 yrs, 1, 70+ yrs, 1	
(h) Duration of illness 10 days, 4, 11 to 15 days, 2, 20+ days, 5, unknown, 2	
E Massive atelectatic collapse	16
(a) Bronchopneumonia, 4, Lobar pneumonia, 12	
(b) Resolution	
(c) Collapse lobe only, 4, Collapse bc only, 11, Collapse of consolidated and uninvolved lung, 1	
(d) Lobes collapsed Rt upper, 1, Rt middle, 2, Rt lower, 4, Rt upper and middle, 2, Rt middle and lower, 3, Left lower, 3, Left lung, 1	
(e) Types I, 5, II, 2, III, 2, V, 4, VI, 1, VII, 1, XIV, 1	
(f) Ages 5 mos, 1, 30 to 49 yrs, 3, 50 to 59 yrs, 4, 60 to 69 yrs, 2, 70+ yrs, 6	
(g) Duration of illness 9 days or less, 9, 10 to 21 days, 4, 30+ days, 3	

parent from the table that several varieties of atelectasis are represented among the cases of both lobar and atypical pneumonia

There was an impressive number of cases in which large portions of the lung were collapsed. In many instances the collapsed portions showed only slight congestion without inflammatory changes while in others there was evidence of resolution and organization with a comparatively small amount of residual exudate. It is not unlikely that acute collapse of such extent may have been the chief cause of death or a major contributing factor in the outcome in some of these patients who had already been suffering from reduced aeration due to the inflammatory consolidation in other lobes.

Abstracts of Cases It is of interest to mention briefly a few cases selected to illustrate special features of atelectasis complicating pneumonia

Case 1 Sudden and violent onset of massive atelectasis during the stage of resolution T. K., a 48 year old man, whose previous history was non-contributory except for a mild illness suggesting "pleurisy" early in 1928, was admitted to the hospital January 18, 1929. On January 1 he had coryza and a dry cough. This lasted one week and was followed by mild diarrhea, malaise, anorexia and headache lasting

another week. On January 15 he had a severe chill followed by sharp pain in the left chest and cough productive of tenacious bloody and later rusty sputum, all of which continued to the time of admission. The physical findings were those of lobar pneumonia of the left lower lobe. Sputum and blood culture yielded Type I pneumococci. Felton's Type I concentrated antibody was given intravenously in small divided doses during the first four days (total of 45 c c). Although the consolidation had spread to involve the entire left lung, there was a gradual subsidence of fever and discomfort. Daily blood cultures after serum therapy remained sterile. The physical signs of resolution were present throughout the left lung on January 24, but the patient remained markedly prostrated. During the night of January 31, the patient was suddenly awakened with intense dyspnea and restlessness, and the pain in the left chest which had previously subsided, recurred with increased severity. These symptoms subsided within a half hour after an injection of morphine. A few hours after this episode the characteristic physical signs of massive collapse of the left lung were present. The breath sounds in the left infraclavicular region were amphoric in character. There was copious mucopurulent sputum. Evidence of resolution returned but the displacement of the trachea and heart to the left side persisted during the patient's stay in the hospital. They were less marked at the time of discharge on March 13, 1929. This patient's course was further complicated by a phlebitis of the left femoral vein accompanied by a low-grade fever beginning February 5 and lasting for two weeks. Numerous sputum examinations during and after the acute illness failed to show tubercle bacilli. The patient was examined one year later, at which time no abnormal signs were made out in the chest. The patient had been symptomless during the intervening 15 months.

A roentgenogram taken on January 19 showed mottled cloudiness of the lower two-thirds of the left chest with the heart and trachea in normal position. Seven films taken at intervals after the attack of acute dyspnea showed the trachea and heart markedly displaced to the left, but those taken before discharge showed definite clearing especially in the lower lobe. A film taken in June 1930 showed the trachea and heart in normal position and the lung fields normal.

Case 2 Latent onset of massive collapse during a severe infection—delayed resolution, and fibrosis of collapsed lung. M W, a 52 year old man, entered the hospital November 12, 1930, with the typical history and physical findings of a severe lobar pneumonia of six days' duration and involving the entire right lung. An upper respiratory tract infection was present for one week prior to the onset. Type I pneumococci were obtained from sputum and blood culture. Large amounts of concentrated antipneumococcus serum were given between November 14 and 20. Repeated blood cultures were positive until November 16 but later ones were sterile. The jaundice, cyanosis, distention, and physical signs of consolidation present on admission continued until November 25. Staphylococcus abscesses and decubitus ulcers developed over the thighs during this time. Thereafter, there was gradual improvement but marked prostration and weakness persisted. On November 21 the physical signs of atelectasis were made out and the trachea and heart were markedly displaced to the right. These signs persisted until the time of discharge, February 10, but much moisture appeared in the affected lung and the lower lobe showed marked clearing. Bronchoscopy was done by Dr L M Freedman on two occasions, during which much mucopurulent material was removed and attempts were made to inflate the lungs, but the collapse remained. The sputum was repeatedly searched for tubercle bacilli but none were found. The patient returned to the hospital six weeks later and another series of four bronchoscopic aspirations and lipiodal injections was done over a period of several weeks. The lower lobe cleared completely but the upper lobe remained contracted and showed definite evidence of fibrosis. The lipiodal failed to enter the bronchi of the upper lobe.



Fig 1

Figs 1 and 2 Roentgenograms in case 2 showing massive pneumonia of the right lung on the sixth day, and retraction of heart and trachea and clearing lower lobe on the thirty-first day

Fig 2

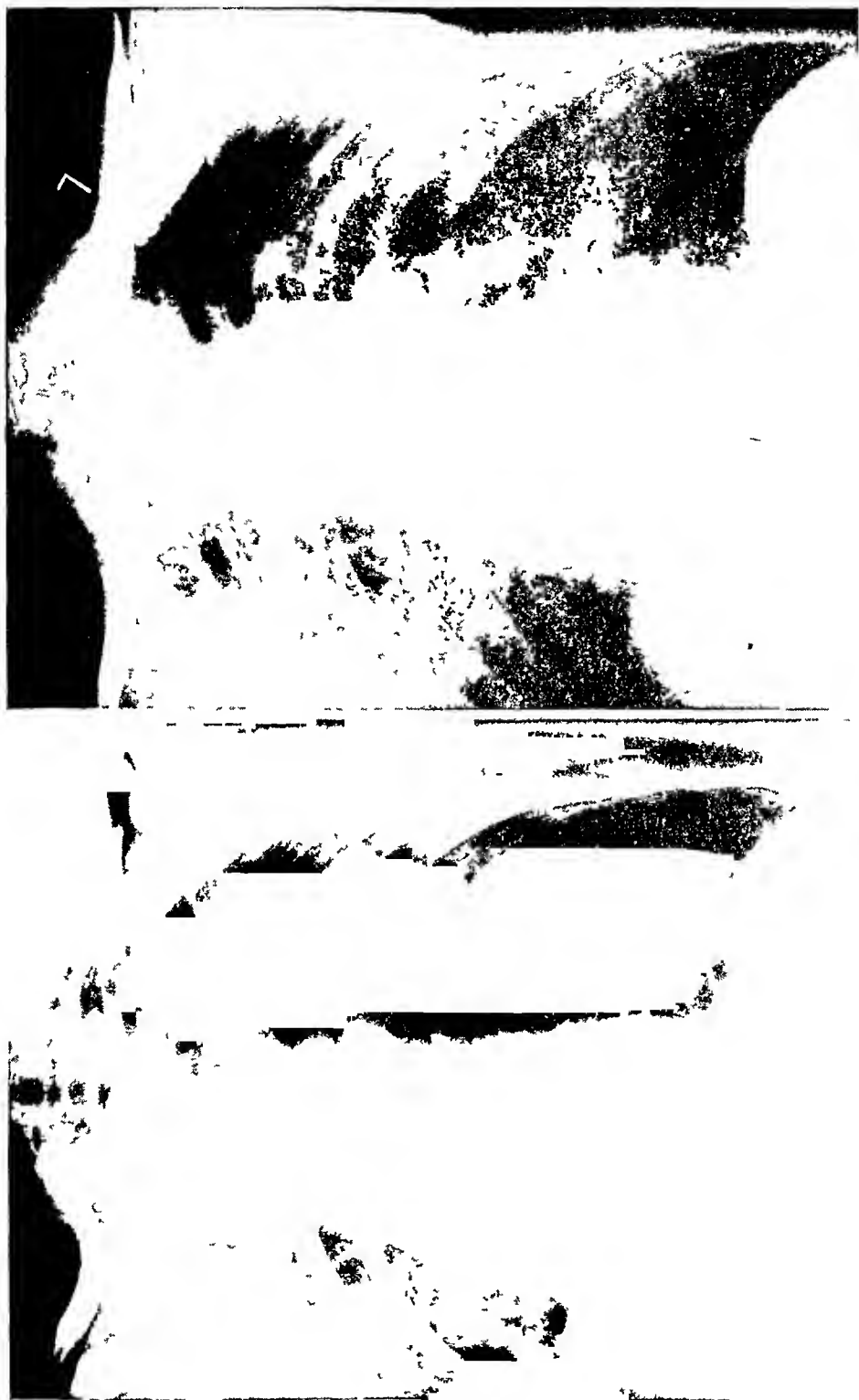


Fig 3

Fig 4

Figs 3 and 4 Roentgenograms taken one and two months respectively after the film in figure 2. Note the high right diaphragm with the heart and trachea on the right in figure 3. There is partial restoration of the heart with evidence of fibrosis in the right upper lung in figure 4 (taken after the sixth bronchoscopy and lipiodol injection).

The first roentgen-ray taken on the day of the earlier admission showed a dense right lung with the heart and trachea in normal position. The next plate taken four days later and numerous roentgen-ray plates taken during the subsequent four months showed the mediastinal contents still displaced to the left, but the later films showed that the lower and middle lobes had cleared and the bronchi to these lobes were outlined by the lipiodal which failed to enter the bronchi of the upper lobe (figures 1 to 4).

Case 3 Latent onset of massive collapse in a patient with pneumonia of moderate severity C J, a 38 year old male, entered the hospital February 11, 1931, with typical lobar pneumonia of four days' duration involving the right lower lobe. He had had a cold and slight cough for four weeks previously. The sputum showed pneumococci which failed to agglutinate with the available antipneumococcus serums, Types I to XX, inclusive, and repeated blood cultures showed no growth. The patient had a mild illness with crisis February 18 after which time the physical signs of resolution alternated with those of fluid in the left lower lobe. During the first week in April the lung cleared almost completely. There was a moderate amount of mucopurulent sputum. Roentgenograms taken on February 12, 15, 18, and 24 and on March 2 all showed pneumonia of the right lower lobe. In the two latter plates the density was quite marked suggesting the presence of fluid. Films taken on March 8, 15, 19 and 30 all showed a markedly elevated right diaphragm, the heart displaced to the right, and the rib spaces on the right contracted but the trachea was not much displaced. A film taken on June 15 showed definite but incomplete clearing of the lung and the heart restored to normal position (figures 5 to 8).

Case 4 Pneumonia complicated by atelectasis and empyema M N, a 34 year old woman with a negative respiratory history except for influenza in 1918, entered the hospital May 20, 1930, at the end of the fourth day of a severe lobar pneumonia involving the entire right lung. Type I pneumococci were found in the sputum and blood culture. The patient received large amounts of specific antipneumococcus serum for four days during which the initial toxemia and dyspnea gradually subsided but sweating, prostration, marked leukocytosis, and the physical signs of fluid appeared and persisted. Later examinations showed the trachea to be markedly displaced to the right and loud amphoric breathing was heard in the right infraclavicular region. The subsequent appearance of coarse moist râles in this area suggested the presence of pulmonary tuberculosis with cavitation. Numerous examinations of the sputum for tubercle bacilli were negative. A roentgenogram taken May 21 showed a dense right lung but the trachea and heart were not displaced. A subsequent plate taken on May 27 and several later ones showed marked atelectasis of the right upper lobe with retraction of the trachea to that side. Signs of resolution appeared in the upper lobe which remained collapsed throughout the 12 weeks' stay in the hospital. She had rib resection and drainage, and the wound healed completely. The patient returned after 18 months at which time no physical or roentgenologic signs of collapse could be demonstrated and the lungs were entirely clear.

COMMENT

No attempt has been made to estimate the frequency with which atelectasis complicates the course of pneumonia. The careful studies of Griffith³ and of Graeser, Wu and Robertson²³ in small groups of cases would indicate that this complication is not infrequent. The cases reported in this paper by no means represent all of the cases of pneumonia in which the condition has occurred in this hospital, but have been selected only because of the definite involvement shown in the roentgenograms or because the condition was noted at autopsy. Minor degrees of atelectasis probably occur at various

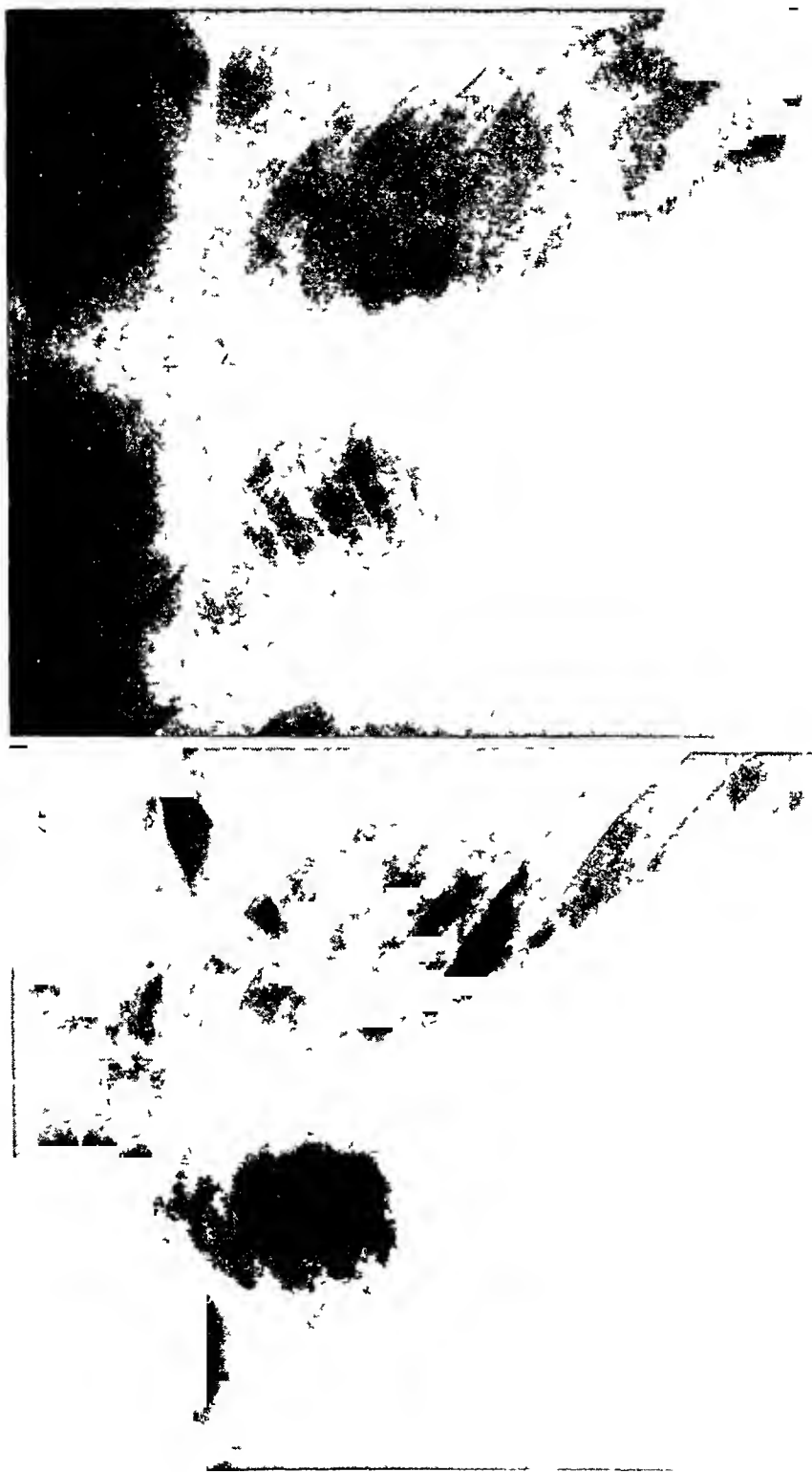


Fig 5

Fig 6

Figs 5 and 6 Roentgenograms taken on the fourth and twenty-third day, in case 3. Note the heart and trachea displaced to the affected side in the second film.



Fig 8 Note the high dia-

Fig 7

Figs 7 and 8 Roentgenograms taken one and four months respectively after the one shown in figure 6 and almost complete clearing in figure 8 phragm and shift of heart and trachea to the right in figure 7

stages in most cases of pneumonia but they probably are of no significance because they are usually temporary and not extensive

The pathogenesis of this condition can be reasonably explained in the light of the present knowledge of the various mechanisms which may bring about collapse of the lung under a variety of conditions. Contraction of the partly consolidated lung early in the disease or of the partly resolved lung later is aided by the occlusion of bronchi with the unexpelled thick exudate, by the reflex inhibition of diaphragmatic movement due to the fibrinous pleuritis and is probably aided by the push of the overdistended normal lung from the opposite side. The shallow breathing during the acute illness which is common during the active disease and which is continued during the subsequent period of prostration is another factor pointed out by Goldite³⁸ and others. In other words, most of the various mechanisms suggested by previous writers may be operative in different individuals or in the same case.

Another possibility suggests itself, namely that previous damage to the lung has resulted in a loss of the normal resiliency and thus predisposes to atelectasis when pneumonia occurs. In the present cases 44 per cent of the patients with collapse gave a previous history of pneumonia, and a history of probable previous pulmonary infection was present in a considerable proportion of the cases reported in the literature, even among those in infants and children. In 1000 consecutive cases of pneumococcus pneumonia in this hospital, a previous history was elicited in only 16.5 per cent³⁹ and a similar frequency of previous pneumonias has been noted by others. It would seem, therefore, that a previous history of pneumonia is more common among those cases complicated by collapse than would be expected. In addition, there were two patients among those included in this study in whose sputum tubercle bacilli were demonstrated during the acute pneumonia, but could not be demonstrated later. Both of these patients recovered and their lungs were apparently normal to physical examination and roentgen-ray except for a slight right apical fibrosis in one of them. Furthermore, in the cases presented in this paper and in those quoted, the right lung, and particularly the right upper lobe, was affected in far more than the usual proportion of cases. This circumstance and the fact that even in many of the cases in children reported in the literature there was a history indicating previous lung infection and the fact that lobes undergoing organization have become collapsed makes this a plausible contributory factor.

Jacobaeus, Lelande, and Westermarck⁴⁰ have suggested another possible mechanism for the production of sudden massive atelectasis, namely a spontaneous spasm and contraction of a bronchus. They noticed appearance of massive collapse of a lobe within 10 minutes after lipiodal injections in certain normal individuals and explained it in this manner. Such a mechanism may be operative in pneumonia.

The cases reported in the literature and those presented here suggest that

atelectasis of the lung may be a frequent complication of primary pneumonia and may serve to explain unusual events or puzzling physical signs or a protracted course in otherwise uncomplicated cases. It may serve to explain the suppression of breath sounds early in the disease and later may be responsible for the signs often interpreted as resulting from thickened pleura or small amounts of fluid in the pleural cavity which cannot be verified by thoracentesis. It may be an important factor in the conditions variously known as unresolved pneumonia, delayed resolution, or organizing pneumonia and contribute to a delay in healing of empyema cavities. The condition may also serve to explain certain sudden episodes of acute dyspnea and sudden deaths occurring during the course of pneumonia or during the stage of resolution. In some instances such sudden deaths may be attributable to pulmonary infarction, a condition not infrequently seen at autopsy. Indeed, in case 1 this possibility is strongly suggested by the later appearance of phlebitis of the femoral vein. The failure of this patient to raise bloody sputum, the appearance of the characteristic physical and roentgenologic signs and the fact that the first evidence of phlebitis appeared only several days later make infarction a less likely explanation of the episode of dyspnea. Furthermore, in none of the cases showing massive atelectasis at autopsy was there evidence of pulmonary infarction.

There is no suggestion from the present cases or from those reported in the literature that atelectasis is an important factor in the pathogenesis of primary pneumococcus lobar pneumonia except possibly in certain cases where the onset of the disease occurs shortly after inhalation of foreign substances such as may occur after a vomiting spell. Such an assumption is not consistent with the definite occurrence of atelectasis during the disease and after the consolidation has already involved part or all of a lobe. The studies of Robertson and his coworkers also fail to uphold such an assumption either in the spontaneous disease in man²³ or in the experimental infection in dogs.⁴¹

SUMMARY AND CONCLUSIONS

- 1 A number of cases of massive atelectatic collapse of the lung complicating primary pneumonia were collected from the literature.

- 2 A group of 62 cases of primary pneumococcus lobar pneumonia in which this complication was noted in roentgenograms was presented.

- 3 A second group of 47 cases of pneumococcus pneumonias in which atelectasis of varying extent and due to a variety of factors was present at autopsy was also considered.

- 4 The significance of this complication was discussed.

- 5 The possibility of atelectasis should be borne in mind in cases of lobar pneumonia and may serve to explain certain otherwise puzzling physical findings, sudden attacks of dyspnea or an unusually protracted course.

- 6 The usual course of events in the characteristic case where the atelectasis complicates convalescence is somewhat as follows. A patient is acutely

ill with typical lobar pneumonia and begins to show gradual evidence of improvement, with lowering of fever and pulse rate and the appearance of moisture in the consolidated lobe indicating resolution. He is suddenly seized with intense dyspnea of short duration after which pleuritic pain, moderate fever, and leukocytosis recur, and the physical signs and roentgen-ray give evidence of elevation of the diaphragm with a shift of the heart, and usually the trachea also, to the affected side. The consolidated lobe may then show signs suggesting fluid or these signs alternating with those of solidification. When the upper lobe is collapsed, the breath sounds are intense and amphonic in character and, as moisture appears, suggest tuberculosis with cavitation. These signs may be present while fluid accumulates in the pleural cavity. The collapsed lobe reexpands within a few days or weeks but organization and fibrosis may leave this affected lobe contracted.

In certain patients, particularly if they are markedly prostrated after a severe course, the signs of collapse may appear during convalescence without an explosive onset.

Collapse of varying degrees occurring during the acute stage of pneumonia may be manifested only by the signs suggesting fluid or by the evidence of displacement of the heart and trachea, or only by careful roentgenographic examination. In such cases the collapse, if it involves the affected lobe, is usually of short duration, evidence of solidification soon appears, and the course of the disease continues. If a previously uninvolved lobe is collapsed, the disease may extend to involve this lobe.

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THE EXOCRINE FUNCTIONS OF THE PANCREAS

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EARLY in my career, interest in medical research problems was aroused through a fortunate association with Dr. Joseph H. Pratt of Boston. It was he who stimulated my investigations on the normal and the pathologic physiology of external pancreatic functions. The results of these investigations furnish the subject matter of the present dissertation.

Important studies on the rôle of the pancreas in digestion began with the work of Claude Bernard,¹ who showed that the pancreatic juice was essential to the process of digestion. Other physiologists of that time were, however, unable to confirm Bernard's observations,² and although many further careful investigations of the digestive function of the pancreas were reported by various observers, especially between the years 1890 and 1911,³ the rôle of the pancreas in digestion remained an unsettled question until the studies of Pavlov.⁴ Pavlov worked with dogs, in which animals he produced the fistulae which bear his name. By means of a fistula he was able to obtain pure pancreatic secretion, in which he demonstrated the presence of proteolytic, amylolytic and lipolytic enzymes. In later years Pratt⁵ and still later McClure and Pratt⁶ convincingly confirmed Bernard's observations that excluding pancreatic secretion from the intestines of dogs was immediately followed by lack of absorption of gross amounts of ingested foodstuffs.

In 1902 Bayliss and Starling⁷ published their observations on the factors concerned in stimulation of external pancreatic secretion. From these observations they postulated the attractive theory that there exists a substance in the intestinal mucosa, designated as prosecretin, which is converted into another substance designated as secretin by action of hydrochloric acid coming from the stomach. They further postulated that the secretin thus formed was absorbed and carried through the blood stream to the pancreas, and after reaching that organ excited its external secretion. The studies of the many observers who have confirmed the experimental observations of Bayliss and Starling have been correlated and are critically presented in a publication of Fairall and Ivy.⁸ Fairall and Ivy working with dogs also studied the effects on the enzymic concentrations of the secretions of a pancreatic transplant of administering different types of foodstuffs. From the results of these studies, together with those derived

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from the critical review of the work of Bayliss and Starling and subsequent experimentors, Fairrell and Ivy⁷ in 1926 confirmed the conclusion previously expressed by the present author⁸, which was that all the studies mentioned established the highly important physiological facts that (1) stimulation of the external secretion of the pancreas is of humoral origin, although the exact mechanism remains unsettled, (2) ingestion of food is followed by the secretion of pancreatic juice, and (3) the external secretion of the pancreas plays an essential rôle in digestion. Since this publication in 1926 Ivy⁹ has succeeded in making a preparation from dogs' duodenal mucosa which he considers contains a hormone possessing the physiological properties ascribed to secretin. This work will be discussed later.

All of the investigations summarized in the foregoing paragraphs have been carried out on lower animals. In how far the results are applicable to man can be determined only by actual observations on human subjects. However, there is pathological evidence confirming the importance of the external pancreatic secretion in man, for example, disease which excludes pancreatic juice from the intestines of man is known to be accompanied by marked disturbances in the digestion and absorption of food. Various investigators have studied pancreatic secretions obtained from operative fistula in man. As the result of such a study Glaessner¹⁰ found that the amount of pancreatic juice secreted was greatly augmented by food. Wohlgemuth¹¹ obtained pure pancreatic juice from a traumatic fistula in a human subject. Other than for the presence of the fistula, the subject's physical state was apparently normal. These studies showed that the ingestion of food consisting largely of fat brought about pancreatic secretion showing the greatest degrees of all types of enzyme action while the secretion following a carbohydrate meal showed the least. On the other hand, carbohydrate meals were followed by the secretion of the largest volumes of pancreatic juice, while fatty foods produced the least. Mocquot, Joltrain and Laudat¹² also found that carbohydrate food produced the greatest amount of pancreatic juice, but that a meat meal was followed by the least. Thus the results of these observations showed the existence of a relation between the kinds of foodstuffs ingested and the amounts of pancreatic juice secreted, and also the concentration of enzymes found in this juice. Kahn and Klem¹³ also found that "There was a different rate for the secretion of the various enzymes and therefore a different rate for the discharge of the total amounts at one time, with corresponding variation in the frequency of renewal of the supply of enzymes of the gland." Wohlgemuth¹¹ and Mocquot, Joltrain and Laudat¹² observed intermittent secretion of pancreatic juice through the fistula, while von Friedrich¹⁴ observed continuous secretion by his patient. Neither these observers nor Poljak¹⁵ were able to demonstrate a relationship between the type of foodstuffs fed and the degree of concentration of the enzyme specific for that kind of food.

The studies on pancreatic secretion of man discussed were all carried out on subjects in more or less pathologic physical states, while the experi-

mental methods employed are open to criticism. Nevertheless, the findings show that in man, as well as in lower animals (1) Ingestion of food is followed by the secretion of pancreatic juice, and (2) the external secretion of the pancreas plays an important rôle in digestion. These findings are obviously of great importance. Nevertheless, they do not establish the mechanism which stimulates the secretion of pancreatic juice nor the conditions under which intestinal digestion actually occurs in the living normal man. It is generally accepted that the end products of intestinal digestion in man are the same as those in lower animals, that is, carbohydrates are converted into monosaccharides, fats into soap and glycerol, and proteins into amino-acids, and that these end products are absorbed as such. However, it should be noted that it was not until the work of Folin¹⁶ and of Van Slyke¹⁷ that the absorption from the gut of the end products of protein digestion was established. It is only fair to add that all the phases of the various processes involved in the digestion and absorption of both proteins and fats are not yet fully established.

There are available but comparatively few studies on the physical and chemical conditions under which intestinal digestion occurs in man. Practically the only studies on the physical chemistry of intestinal digestion in the living normal human subject are those of McClendon et al.,¹⁸ Hume, Denis, Silverman and Irwin¹⁹ and that of the present author and his co-workers which will be discussed later. In fact many of the conditions affecting enzyme action were not established until the publication of the work of Sorensen²⁰ in 1909. This work permitted the development of reliable methods for indirectly quantitating enzymes present in pancreatic juice, first by McClure²¹ and then later by Willstätter²² and Ivy^{9,23}. These methods, the roentgen-ray, electrometric apparatus, the duodenal tube, together with advances in physical chemistry and biochemistry, permitted the development of procedures and methods for studying digestion in the living man. The most extensive systematic studies of this subject were carried on first by McClure and co-workers²⁴ and later by Christiansen of Copenhagen²⁵. Several studies on man have been made by Chiray²⁶ and less extensive observations by other investigators, these studies will be discussed later. The clinical importance of all these various studies is due primarily to the objective demonstration of phenomena occurring in normal human subjects which will permit comparisons with those occurring under similar experimental conditions in abnormal subjects. The explanations of the mechanisms of functional activities producing the phenomena are of only indirect value in the actual use of the tests in medical diagnosis. This indirect value lies in the fact that usually, but not always, the more nearly correct the physiological basis for a clinical test or procedure the more reliable are the results for diagnostic purposes. Thus, the interpretations of results of investigations made for clinical purposes may be, indeed often are, radically different from those which are of value in the medical sciences.

Long experience in clinical medicine, clinical research and investigations in pure science have led the present author to conclude that the investigator who has not had a considerable experience in the actual practice of medicine rarely is capable of the type of interpretation required for purposes of clinical diagnosis. In relation to human medicine both physiology and pathologic physiology may be, therefore, approached from two viewpoints. The discussion of the physiology and pathologic physiology of the pancreas, which follows, is from the viewpoint of the practitioner of medicine.

In pursuit of clinically applicable studies of the physiology of intestinal digestion in normal man suitability of analytical methods and proper experimental procedures and conditions are of essential importance. Such methods, procedures and conditions were developed by the present author and co-workers and on them depends very largely the reliability of the studies whose discussion follows.

One of the problems was whether or not reliable means could be developed for demonstrating pancreatic stimulation by examination of duodenal contents. The measure of pancreatic activity chosen by the present author was that of enzymic concentration, while Christiansen²⁵ selected the quantity of enzymes secreted. The results obtained by both of us showed that stimulation of the enzymic function of the pancreas could be demonstrated by examination of duodenal contents obtained under suitable experimental conditions and analyzed by proper methods.

THE EFFECTS OF FOODSTUFFS ON CONCENTRATION OF PANCREATIC ENZYMES

The present author's studies²⁷ showed that pancreatic juice containing variable concentrations and amounts of enzymes is obtainable from the normal human duodenum during the fasting state. It was further found that following cessation of stimulation of the pancreas the juice secreted again assumed the characters of that obtained during the fasting state. Stimulation was characterized by a much greater average concentration of the three types of enzymes and by a greater uniformity in the degrees of enzymic concentrations.

Observations were made to determine possible variations in the concentrations of the various enzymes during different periods in which the secretion of pancreatic juice was stimulated by ingested foodstuffs. For this purpose normal subjects were fed pure protein, and duodenal contents were collected over relatively short intervals during the period of pancreatic stimulation. This study showed that in different fractions of duodenal contents collected from the same subject the concentrations of the same type of enzyme remained fairly uniform. Further observations on the uniformity of enzymic concentrations were made on specimens of duodenal contents collected over hourly periods from normal subjects. The meals were of such size that the minimum emptying time of the stomach as determined

by fluoroscopic examination was more than four hours. This permitted the collection of not less than four specimens from each subject. The study showed that each of the several types of enzyme varied moderately in the degrees of its concentration in the different hourly specimens of duodenal contents from the same subject, but that there was no regular manner in which the variations occurred, that is, there was no constant systematic increase in the enzymic concentrations throughout the period of pancreatic stimulation.

Studies were made to ascertain whether the greatest degree of concentration of a given enzyme occurred in the presence of a meal composed of a type of foodstuff corresponding to its substratum. For this purpose normal subjects were given at different times a meal composed of various pure proteins, fats or carbohydrates. The results showed conclusively that no one kind of pure foodstuff stimulates the greatest concentration of its specific type of enzyme. Christiansen²⁷ made similar findings in relation to the amounts of enzymes secreted under comparable experimental conditions. In addition to the studies discussed, a series of normal subjects was subjected to intraduodenal administration of pure foodstuffs²⁸. The latter were cottonseed oil, special preparations of casein and of beef furnished by the Arlington Chemical Company and dextrose. The oil was mixed with water and the other substances dissolved in water and then introduced into the duodenum through the duodenal tube. Foodstuffs thus administered produced in the same subject enzymic concentrations of duodenal contents entirely comparable to those obtained after their oral administration. After intraduodenal administrations the bile and gastric fractions of the collected duodenal contents were analyzed as well as the pancreatic fraction. The findings apparently eliminated the possibility of the volume of one fraction masking the effects of the other fractions through dilution, because the increases or decreases in the analytical figures rarely failed to coincide.

The foregoing studies show (a) There is a period following the ingestion of foodstuffs during which definitely increased concentrations of pancreatic enzymes are demonstrable in the pancreatic juice collected from the duodenum of man, this period is the result of stimulation of the activity of the external function of the pancreas. During this period of stimulation the concentration of each type of enzyme varies much less than in duodenal contents collected either before or after stimulation. Christiansen found an increase in the amounts of enzymes secreted during this period.

(b) In duodenal specimens collected over succeeding periods during which pancreatic stimulation is in process the enzymic concentrations remain fairly uniform in degree.

(c) The greatest degree of concentration of a given enzyme is not governed by the type of foodstuff corresponding to the specific substratum in which the enzyme acts. However, the degrees of concentration of all

types of pancreatic enzymes are related to the kind of foodstuff fed, oil giving the greatest degree and carbohydrates the least. Christiansen also found well defined relationships between the amounts of enzymes secreted and the type of foodstuff administered.

In relation to clinical diagnosis these findings are important not because of the physiological implications, which will be discussed later, but because they furnish norms with which the findings obtained from pathological subjects can be compared.

EFFECTS OF INORGANIC SUBSTANCES ON CONCENTRATION OF PANCREATIC ENZYMES

Having established the rôle played by foodstuffs on the external secretory activity of the pancreas it was considered of equal importance to study the effects of representative inorganic substances. The substances chosen were distilled water, chemically pure hydrochloric acid, phosphoric acid, sodium phosphate and magnesium sulphate.

Comparative studies^{7, 8, 28, 29} of the degrees of enzymic concentration were made in duodenal contents derived from the fasting duodenum, after the ingestion of tap water and after drinking weak cornstarch solution. For this purpose the fasting duodenal contents were collected over periods of 30 minutes from normal subjects, then 50 c c of tap water were given and the contents collected for two hours, in fractions of one hour each. The enzymic concentrations of the two fractions were comparable. The results representative of those obtained from this comparative study are outlined in the following table. To the table are added the figures representing the enzymic concentration of duodenal contents collected after the ingestion of a mixture of olive oil and tap water. The experiments with the oil feedings and those with the fasting duodenum and tap water feedings were made on separate days.

TABLE I

Enzymic Concentrations of Duodenal Contents Collected from the Fasting Duodenum and after the Ingestion of Tap Water, or of Cornstarch Solution or of Olive Oil

Enzymic Concentration			Food Ingested
Proteolytic in mg N P N	Lipolytic in c c N/10 NaOH	Amylolytic in mg glucose	
1.8	0.5	0.3	Fasting duodenum
5.7	3.5	2.6	25 c c of olive oil and 25 c c tap water
2.7	0.0	0.0	50 c c 0.5% cornstarch
1.5	0.1	0.0	50 c c tap water

In the above table comparison of enzymic concentrations of the contents of the fasting duodenum with those found after drinking water shows that after the ingestion of water or weak cornstarch solution the degrees of con-

centration of the various enzymes present in the duodenal contents are comparable with those present in the fasting contents. However, after the ingestion of olive oil, the degrees of action of all these various enzymes were increased in the duodenal contents of each subject.

Comparative studies were made of enzymic concentrations of duodenal contents obtained after the ingestion of olive oil and of various hydrochloric acid mixtures. The determinations were made in duodenal contents from normal subjects. Results representative of those obtained in a series of experiments are outlined in the following table.

TABLE II

Enzymic Concentrations of Duodenal Contents Obtained after the Ingestion of Hydrochloric Acid and Olive Oil

Enzymic Concentrations			Food Ingested
Proteolytic in mg N P N	Lipolytic in c c N/11 NaOH	Amylolytic in mg glucose	
4.3	1.2	1.2	100 c c N/10 HCl and gum arabic
2.2	0.0	0.2	60 c c N/10 HCl and gum arabic
2.7	0.7	1.4	50 c c N/10 HCl solution
5.7	2.5	2.5	25 c c each of olive oil and water

Study of the table shows that the greatest enzymic concentrations were obtained in duodenal contents derived after the ingestion of olive oil, and that acid was a much less potent stimulant. The latter acted comparably to water. This is to be anticipated because ingestion of water stimulates the production of acid gastric secretion. Observations in which phosphoric acid was used instead of HCl gave results comparable to those described for the latter acid.

Studies²⁸ were made on five normal subjects of the comparative stimulative effects of foodstuffs, HCl and $MgSO_4$ solutions in the secretions of pancreatic juice. These subjects were given, in aqueous suspension, 100 c c of 50 c c pure cottonseed oil, or a solution of one of the following substances, 50 grams of fat-free beef peptone, 50 grams pure dextrose, 8 grams of $MgSO_4$ crystals or N/40 HCl. Results representative of those obtained are outlined in the following table.

The findings of this study, represented in table 3, show that magnesium sulphate is a more potent stimulant to the secretion of pancreatic enzymes than is HCl solution or dextrose. They also clearly show that inorganic substances, including HCl, are less potent stimulants to the secretion of pancreatic enzymes than are fats or protein foodstuffs.

The studies which have been briefly described show that the inorganic substances, hydrochloric acid, phosphoric acid and water, are weak and inconstant stimulants to the flow of pancreatic enzymes. Magnesium sul-

TABLE III

Minimum and Maximum Concentrations of Enzymes and Chlorides of Duodenal Contents before and after Intraduodenal Administration of Cottonseed Oil, Beef Peptone, Dextrose, HCl and MgSO₄

Test Meal	Pancreatic Enzyme Concentrations						Pepsin Concentration		Chloride Concentration	
	Trypsin		Lipase		Amylase					
	Mini- mum	Maxi- mum	Mini- mum	Maxi- mum	Mini- mum	Maxi- mum	Mini- mum	Maxi- mum	Mini- mum	Maxi- mum
Fasting	1.3	4.2	0.2	1.2	1.9	3.6	0.7	1.0	5.9	6.4
MgSO ₄	3.9	4.6	0.8		0.9	1.4	0.9	1.1	5.2	7.0
HCl	3.8		0.8	1.0	0.7		0.7		4.2	
Dextrose	3.3		0.5		0.7		1.6		4.1	
Peptone	9.5		1.0		3.6		2.0		8.5	
Oil	5.7	8.6	1.2	1.5	4.0	4.5	0.6	1.0	5.2	7.0

phate was a more constant and potent stimulant than were these other substances, although it fails to stimulate in about 20 per cent of normal subjects. At the best, magnesium sulphate was a much less reliable and less powerful stimulant than either fat or protein foodstuffs.

The action of these inorganic substances on the exocrine pancreatic function is comparable to that described by Ivy⁹ after parenteral administration of a substance designated purified secretin. In relation to clinical medicine the studies on inorganic substances are important because they show that such compounds are not satisfactory stimulants when the pancreatic fraction of duodenal contents is examined for diagnostic purposes.

ALKALI SECRETORY ACTIVITY OF PANCREAS

The studies which have been discussed showed that different types of stimulants reacted differently on the external enzymic functions of the pancreas. Obviously, these findings explain the logic of studying the effects of various types of stimulants on the alkali secretory activity of the pancreas. For this purpose pH and buffer values of duodenal contents were determined.³⁰ All pH determinations were made electrometrically. The buffer values were determined by titrating duodenal contents either with tenth normal hydrochloric acid or with sodium hydroxide solution, according as to whether the original material was alkaline or acid. This was accomplished by bringing a definite quantity of the duodenal contents to the neutral point by the addition of standard acid or alkali, the pH values being determined initially and the neutral point evaluated by further potentiometric comparisons, after addition of successive portions of titration solutions. Studies were first made on duodenal contents collected from normal subjects in the fasting state, and then after ingestion of tap water. The pH values obtained during fasting were 6.0 to 8.1 and after water drinking were 7.6

to 8.3, which indicates that water drinking caused some stimulation of alkali secretion. After these preliminary studies the subjects were fed pure foodstuffs or mixtures of them. Duodenal contents were collected during the period of stimulation of the pancreatic juice and pH determined. It was found that duodenal contents derived after the ingestion of olive oil or of arrowroot starch were alkaline (pH above 7), the pH varied from 7.2 to 8.1. On the other hand, duodenal contents collected after ingestion of the protein, edestin, or the mixture of foodstuffs containing edestin were acid (pH below 7), the pH varied from 3.2 to 6.7. The correctness of these findings has been verified by others^{18, 19, 21, 22, 23}. The buffer values of the duodenal contents obtained after administration of foodstuffs were surprisingly uniform. Such uniformity indicates that the physical chemical factors governing the buffer conditions were approximately the same in all specimens of duodenal contents, i.e., the findings indicate that the various types of food substances had about the same stimulating effect on the production of buffer substances. Obviously, this finding indicates that foodstuffs stimulate the alkali secretory activity of the pancreas in a manner differing from their stimulation of the enzymic activities.

The determinations of the pH values discussed above do not afford data concerning the rapidity with which gastric chyme is neutralized within the duodenum. In order to obtain such data⁸ duodenal contents for pH determinations were obtained by aspiration from the first portion of the duodenum, the metal tip was either just beyond the distal end of the sphincter, or within the sphincter. Collections were made over periods of a few seconds to several minutes, depending on the time necessary to collect a quantity sufficient for potentiometric purposes, about 5 c.c. A second duodenal tube was placed in the stomach in order to prove that the ingested meal gave rise to an active flow of acid gastric juice, the acidity being determined by titration and electrometrically. The substances fed were olive oil and N/10 HCl. These studies showed that the acidity of gastric chyme is neutralized the instant it reaches the duodenum and that the neutralization occurred in the region of the pyloric sphincter. The neutralization may be compared to that produced by pouring an acid solution onto the surface of an alkaline fluid with diffusion downward.

Independent stimulation of the two types of pancreatic secretions, alkali and enzymic, was studied further. For this purpose enzymic concentrations of duodenal contents were determined after the ingestion of olive oil and various mixtures of hydrochloric acid. The results of these studies showed that only an indifferent relationship existed between the enzymic secretory function of the pancreas and the alkali secretory function. The independence of these two secretory activities is also maintained by other observers^{23, 24, 25}. The studies on the alkali secretory function of the pancreas furnish normal findings with which those on abnormal subjects may be compared.

MECHANISM OF PANCREATIC STIMULATION

The foregoing findings which have been discussed furnish data not only applicable to clinical studies but also relating to the factors concerned in stimulation of the external secretory functions of the pancreas. Such stimulation is usually attributed by physiologists to the hypothetical hormone designated secretin. Bayliss and Starling⁶ proposed this theory on the basis of two observations. First, they found that when acid is applied to a denervated loop of the upper jejunum the pancreas secretes. Second, they also found that acid extracts of the duodenal and jejunal mucosa contained a substance called by them, "secretin," which excites the pancreas to secrete when injected intravenously. However, substances possessing the action of "secretin" have been found in many animal tissues other than duodenal and jejunal mucosa and its extraction with hydrochloric acid might very well form various compounds (due to decomposition of proteins, etc.) whose parenteral administration would stimulate the secretion of pancreatic juice. A concise critique of the animal experimentation relating to hormonal stimulation of the pancreas is reported by Farrell and Ivy⁷, together with the observation that they were able to stimulate the secretion of pancreatic juice by a denervated autotransplant of the pancreas in the dog. Their conclusion confirms the opinion of the author that the work of Bayliss and Starling indicates humoral stimulation but not necessarily hormonal stimulation. In more recent studies Ivy⁸ produces stimulation of the flow of pancreatic juice in dogs and in man by the parenteral administration of a preparation designated as a purified secretin. These findings apparently establish a humoral stimulation of the exocrine functions of the pancreas in both lower animals and in man.

The establishment of the chemical (humoral) stimulation of the exocrine functions of the pancreas is of sufficient importance to justify the large amount of experimentation carried on by various observers during the past 32 years. However, merely because a parenterally administered substance stimulates pancreatic secretions does not prove the existence of a hormonal (secretin) mechanism of such stimulation. Realizing this, Ivy made further investigations⁹ in which he found that his purified secretin and also various foodstuffs failed to influence the enzymic concentrations of pancreatic juice of dogs. Obviously, these findings favor the correctness of the hormonal (secretin) stimulation in dogs. However, although Ivy's purified secretin⁹ did not affect the concentrations of pancreatic enzymes in man, the investigations of the present author and others have unquestionably established that such concentrations are definitely affected by various foodstuffs. These reported differences suggest that there possibly exist differences in the mechanisms of pancreatic stimulation in dog and man. It would be logical to postulate that the carnivora require only a restricted type of pancreatic stimulation since protein is the predominant foodstuff, while omnivora might require more complicated mechanism because of the various

elements habitually entering into their diet. Another important fact is that the experimental observations have always been made on animals whose physiological states have been drastically modified. These considerations make it seem hazardous to conclude from experimental data now available that the mechanisms of stimulation of the exocrine functions of the pancreas in man are necessarily similar or indeed comparable to those in lower animals.

There are various studies made by the author and Christiansen the results of which are not compatible with the secretin theory of stimulation of the pancreas. It will be recalled that the secretin theory postulated an acid state of duodenal contents. However, studies discussed above show that the duodenum during digestion is either alkaline or the amount of free HCl is not more than a trace. Certainly hydrochloric acid could not have played a role in the stimulation of the pancreas in the author's patient with achylia gastrica, the gastric contents were kept alkaline by mixing sodium hydroxide with the foodstuffs fed. These findings negate the application of the secretin theory, as usually described, to man. Measuring the production of enzymes in terms of enzymic concentrations shows such production to be governed by the type of stimulant administered. Were pancreatic stimulation in man the result of only the one substance, secretin, the consistent variations which have been found for different types of stimulants would not be anticipated.

Both Ivy⁹ and Chiray¹⁰ found that the parenteral administration of substances designated by them as purified secretin stimulated an increase in the amount of pancreatic juice secreted by normal men. Chiray also found an increase in the concentration of enzymes, while Ivy did not. The difference in findings is logically explained as due to differences in the substances administered. These findings are evidence favoring the correctness of the conclusions drawn independently by the present author and by Christiansen, which is that the alkali and enzymic activities of the pancreas are independent functions. The author's studies^b of this problem were made on normal young men. The subjects were fed water, hydrochloric acid, olive oil mixed with hydrochloric acid, and olive oil mixed with water. Two tubes were used simultaneously, the tip of one entering the duodenum and the tip of the other remaining in the stomach. The latter tube permitted it to be shown that the contents of the stomach were actively acid throughout the experimental observation periods. Throughout these periods gastric acidity was titrated and electrometric pH determinations were made of the gastric and duodenal contents together with estimations of the concentrations of the pancreatic enzymes. These findings showed that water and hydrochloric acid solutions stimulated the secretion of alkali by the pancreas but produced no demonstrable effect on the concentration of enzymes. On the other hand, the olive oil meals stimulated both the alkali and enzymic fractions of pancreatic juice, the gastric contents being actively acid. These

findings indicate that the two exocrine pancreatic functions react differently Christiansen ²⁵ investigated the subject with unique experimental procedures From his studies he concluded that the secretion of alkali and the secretion of enzymes represent independent functions

PATHOLOGIC PHYSIOLOGY OF EXTERNAL PANCREATIC FUNCTION

The experimental findings and their relation to the mechanisms of external pancreatic functions which have been discussed furnish a basis for the study of abnormal pancreatic conditions, whether functional or organic In making such studies propriety of experimental methods and procedures is of essential importance Those developed and used by the present author will be discussed in connection with the considerable number of other procedures which have been proposed for the purpose of eliciting evidence of pancreatic involvement Critical review of them demonstrates that they are designed to show functional disturbances in the pancreas either directly or indirectly through the secondary effects on metabolism They may be classified as follows

- I Test for demonstrating the secondary effects of pancreatic function
 - A Effect on carbohydrate metabolism
 - 1 Glycosuria
 - (a) Dynamic
 - (b) Potential
 - 2 Cammidge pancreatic reaction ³⁷
 - B Unclassified effect on metabolism
 - 1 Loewi mydriasis test ³⁸
 - C Effect on alimentation
 - 1 Steatorrhea and percentage of undigested fats ^{3, 39, 40}
 - 2 Azotorrhea and creatorrhea ^{41, 42}
 - 3 Urinary ethereal sulphates
- II Direct tests for pancreatic function
 - A The estimation of the concentration of pancreatic enzymes in vitro (quantitative)
 - 1 Estimation in excreta
 - (a) Trypsin in feces ^{43, 44 45}
 - (b) Diastase in feces ^{46, 47 48}
 - (c) Lipase in urine ⁴⁹
 - (d) Diastase in urine ⁴⁷
 - 2 Estimation in gastric contents
 - (a) Trypsin, diastase and lipase after an oil meal ^{50, 51}
 - 3 Estimation of enzymes in duodenal contents
 - 4 Estimation in blood
 - (a) Diastase ^{47 52 53}
 - (b) Lipase ^{54 55}

B The estimation of the concentration of pancreatic enzymes in vivo

- 1 Keratin coated capsules containing methylene blue ⁵⁶
- 2 Glutoid capsules of Sahli containing iodoform ⁵⁷
- 3 Nucleus test of Schmidt, ⁵⁸ and the modifications of Einhorn, ⁵⁹ and Kashiwado ⁶⁰

Descriptions of these various tests are found in the encyclopedic work of Weiss ⁶¹ and in other publications ^{59, 11, 12, 62}

Of the above tests but few have proved to be of practical value. Steatorrhea, azotorrhea and creatorrhea occur in the presence of advanced disease of the pancreas. In the presence of complete exclusion of pancreatic juice the nucleus test may still be positive. Of the various examinations of substances in the blood the most efficient ⁶³ is the test for lipase devised by Cherry and Crandall ⁵⁵. In relation to lipase in the blood, it is of interest to note the work of Boldyreff ⁶⁴. This investigator has concluded from experimental observations that the external pancreatic secretion furnishes enzymes to the blood. Both Boldyreff ⁶⁴ and Oelgoetz ⁶⁵ attribute great importance to this phenomenon. However, neither of these observers has given consideration to the rôle played by the liver in destroying pancreatic enzymes reaching it in the portal blood, which phenomenon is discussed by Fischler ⁶⁶. Examination of the pancreatic moiety of duodenal contents furnishes the most useful information concerning the functional state of the pancreas. The reliability of such examinations depends (*a*) on the correct use of the duodenal tube, (*b*) on procedures which insure the collection of representative specimens of duodenal contents, (*c*) on the use of a stimulant which will uniformly cause secretion of pancreatic juice and (*d*) on analytical methods incorporating the necessary physiochemical principles. The present author has developed a system of duodenal analysis ²¹ which incorporates all these requirements. Sufficiently large numbers of normal and pathological subjects have been studied to establish the status of this system. In brief the method consists of giving the duodenal tube with the subject in the fasting state, and verifying the position of the tip of the tube by fluoroscopy. Cream or oleic acid is used to stimulate pancreatic secretion, and a specimen is then collected which is representative of the duodenal contents during the period of such stimulation. The specimen is analyzed for enzymic activities by the methods devised by the author, these incorporate the necessary physiochemical principles. Willstätter ²² and also Ivy ⁹ have developed reliable analytical physico-chemical methods for estimating enzymic activities. The status of the results obtained from the author's system of duodenal analysis in relation to clinical diagnosis was established by the study of large numbers of patients representing a considerable variety of diseases. Results representative of those obtained in patients suffering from organic pancreatic affections are outlined in the following tables.

TABLE IV

Representative Duodenal Enzymic Concentrations in Pancreatic Disease

Subject	Proteolytic non-protein nitrogen mg	Lipolytic N/10 NaOH c c	Amylolytic glucose mg	Diagnosis
Normal controls	20	10	10	
4*	50	02	04	Acute pancreatitis convalescing
	19	07	19	
3*	11	03	05	Chronic pancreatitis
	08	03	03	
2*	00	02	20	Cancer head of pancreas
1*	25	16	20	Cancer of body and tail of pancreas

* Laparotomy

The effects of pancreatic disease on the enzymic concentrations of duodenal contents, demonstrated by studies comparable to those outlined in table 4 together with those reported by other investigators⁶⁷ may be summarized as follows

Extensive involvement of the pancreatic parenchyma, due to acute pancreatitis or less extensive pathologic lesions accompanying chronic pancreatitis, is associated with a decrease below the minimum normal limits of at least two of the three types of enzymic concentrations in the duodenal contents. It is possible that the diminution in enzymic concentrations in some of these cases is due, in part, to obstruction to the flow of pancreatic secretion by the pathologic process, as well as to actual destruction of pancreatic parenchyma.

Cancer of the head of the pancreas produces a marked decrease in enzymic concentrations, although extensive carcinomatous involvement of the pancreas, not involving the head or the duct of Wirsung, does not demonstrably affect the enzymic concentrations of duodenal contents.

Slight involvement of the pancreatic parenchyma, when due to acute pancreatitis or pancreatic cyst, does not affect the enzymic concentrations of the duodenal contents.

The functional state of the pancreas, as reflected in changes in enzymic concentrations in duodenal contents, was investigated⁶⁸ in patients suffering with diseases of the liver or gall-bladder. In chronic cholecystitis, with or without gall stones, about 50 per cent of the cases showed slight abnormality in pancreatic enzymic function. This was most often expressed as a diminution in the concentration of lipase. The presence or absence of jaundice exerted no demonstrable influence on pancreatic function. Comparable evidence of pancreatic functional disturbance was demonstrated in 95 per cent of the patients who had undergone cholecystectomy. Calculous obstruction of the ampulla of Vater will produce low enzymic concentrations. These findings have been verified

by others^{67, 69} Very abnormal enzymic concentrations were also found in acute cholecystitis. However, normal enzymic concentrations were found in cancer of the bile ducts which did not involve the pancreatic ducts. Mild disturbance of pancreatic function was found in 70 per cent of patients with cirrhosis of the liver and in 50 per cent of patients with toxic jaundice. Only about 16 per cent of patients with uncomplicated duodenal ulcer gave evidence of mild pancreatic dysfunction.

The combined study of the pancreatic and biliary moieties of duodenal contents has been found of value in differentiating between benign and malignant causes for jaundice and in localizing the site of the lesions. The important findings in such differentiation may be outlined as follows.

Normal enzymic concentrations and no bile demonstrate that the lesion is in the biliary tract above the ampulla of Vater. If bile reappears after repeated instillation of magnesium sulphate solution into the duodenum it is highly probable that the obstruction of the biliary tract is of benign character. The more concentrated the bile that is obtained, the more probably benign is the lesion. But if bile does not reappear, the chance that the lesion is benign is much more remote.

Abnormal enzymic concentrations, with the initial presence of bile, especially if the bile is relatively concentrated, or if it reappears after intraduodenal instillation of magnesium sulphate solution, suggest benign obstruction in the region of the ampulla of Vater. In such cases the reappearance of bile may be accompanied by increase in enzymic concentrations.

Abnormal enzymic concentrations, when bile remains absent from the duodenum in spite of repeated intraduodenal administration of magnesium sulphate, suggest cancer of the head of the pancreas.

Duodenal contents grossly discolored with blood, with abnormal enzymic concentrations, and containing no bile denote cancer involving the head of the pancreas, common bile duct and wall of the duodenum.

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VITAMIN C AND INFECTION¹

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INTRODUCTION

THE conception that scurvy has an important relationship to infection is far from new. In fact, some of the earliest descriptions of scurvy bear witness to this relationship and account for the fact that scurvy was often considered an infectious disease. Echthius, whose comments on scurvy were published in 1585,¹ is referred to by James Lind² as follows: "Echthius seems to be the first who gave rise to the opinion of its being a contagious or infectious *lues*. He was led into that mistake by observing whole monasteries who lived on the same diet, and in the same air, at once affected with it, especially after fevers, which no doubt might become infectious in close and confined apartments. He imagined, therefore, that a scurvy might in a manner be the *crisis* of a fever, which as such he deemed contagious." This relationship was more clearly recognized by Maynwaringe,³ a century later, who wrote: "That Feavers and Scurvy do commute and complicate, daily experience doth manifest to Learned Physicians, that are *critical* observatoirs and those intermitting *Feavers*, called *Agues*, which are looked upon and accounted by the vulgar and unknowing, as trivial slight diseases, and, as I have heard some say, *An Ague in the Spring is as good as Physick* but they little consider what *ruine* these *Agues* bring to the best tempered bodies, what alteration and change they make in the *mass* of blood, seldom recovering its former state and purity, if they continue long and neglected and at their cessation and departure you think all is done, the danger and the *prejudice* past, and you *in statu quo prius*, but now begins the *Scurvy* to act its part, sliely and gradually to creep upon you, except by the advice of a skillful Physician, you raze out the *vestigia* of the former disease, *characterized* and *impressed* upon the *Viscera* for nutrition, by *alienating* their ferments from their genuine and *primitive* natures, from which *seminaries* the *Scurvy* will spout forth

"Hereby you may perceive the succession and commutation of diseases, how one disease *introduceth* and is the *preludium* to another."

However faulty may have been the reasoning of the early commentators as to the fundamental cause of scurvy their observations on the effect of

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infections in precipitating the disease have been repeatedly confirmed. Time after time epidemics of scurvy have been seen to sweep through an inadequately fed populace on the heels of a contagious disease. As recently as 1917 this phenomenon was reported from the prison camps of the Central Powers.⁴

Of late years, improvement in the dietary of the poorer classes has been sufficient to make scurvy a relatively uncommon condition confined largely to infants, solitary living bachelors, alcoholics, and patients on certain rigid diets, such as for peptic ulcer. Even in individual cases, however, the influence of infection in unmasking a latent scurvy is often manifest. As Hess⁵ has remarked, "Infection is the most important condition which may suddenly and precipitously induce scurvy."

The chemical isolation of vitamin C or ascorbic acid and the subsequent development of methods for its quantitation in plant and animal tissues have made it possible to study its metabolism in health and disease in a more exact way than hitherto. Vitamin C is a powerful reducing agent and its ability to reduce 2,6-dichlorophenol-indophenol under suitably controlled conditions has been shown to be highly specific.^{6,7} With this dye vitamin C can be titrated directly in the urine or in the protein-free filtrate of blood serum or plasma.

It has been observed that in normal individuals the blood serum level of ascorbic acid is between 0.7 and 2.5 mg per 100 cc, and even within this normal range differences can ordinarily be accounted for by differences in dietary intake of vitamin C.⁸ Elimination of vitamin C from the diet has been observed to be followed by a gradual fall in the blood level of the vitamin until it reached a value as low as 0.2 mg per 100 cc.⁹

The urinary excretion of vitamin C is in the normal healthy subject dependent upon the dietary intake.^{9,10,11} Although observations on the serum level or urinary output of vitamin C in infection have been few and contradictory,¹²⁻²¹ experimental evidence has been accumulating that there is an increased demand for the vitamin in infection. Rinehart²⁰ has shown that this is the case in active rheumatoid arthritis and rheumatic fever, and Heinemann²¹ has confirmed this in other infectious diseases. However, studies of the vitamin C metabolism in a large series of cases with infection are lacking. The purpose of the observations reported here was to seek evidence in regard to the effect of infection on the vitamin C metabolism by estimating the blood ascorbic acid in a large group of hospital patients and controls, and by "balance" experiments in a few patients with infections.

METHODS

The reduced ascorbic acid in the blood serum was determined by the method of Taylor et al.²² Repeated estimations have shown an accuracy of 0.2 mg per 100 ml of blood serum. The data presented were collected from 165 individuals representing a cross section of the hospital population.

including, as controls, members of the staff and technicians, as well as patients without infections

These individuals have been arbitrarily divided into four groups. Group I consists of individuals free from infection who had been on a diet containing some fresh fruit or green vegetables. Group II consists of patients with infections who had been on a diet containing some fresh fruit or green vegetables. Group III consists of patients free from infection who had been on diets lacking in fresh fruits and green vegetables. Group IV consists of patients with infections who had been on diets lacking in fresh fruits and green vegetables.

The first group ("adequate" vitamin C intake without infection) was composed of 43 individuals from all walks of life, the majority of whom were ward patients in the hospital. The average serum level of ascorbic acid in this group was 1.31 mg per 100 c.c. with a range from 0.51 to 2.42 mg per 100 c.c.

The second group ("adequate" vitamin C intake with infection) consists of 66 patients suffering from various infections such as lobar and bronchopneumonia, acute upper respiratory infection, tonsillitis, rheumatic fever, acute gonorrheal arthritis, pyelitis, cystitis, pulmonary and pleural tuberculosis, bronchitis, lung abscess, malaria, acute catarrhal jaundice, staphylococcus abscesses, typhoid fever, streptococcus septicemia, and osteomyelitis. No patient was included who did not exhibit either fever or leukocytosis. The average level of serum ascorbic acid in this group was 0.64 mg with a range from 0.10 to 1.19 mg per 100 c.c. This is about one-half the average value found in the normal group. No correlation between the severity or etiology of the infection and the level of ascorbic acid in the blood was noted except that all of the cases of uncomplicated pyelitis or cystitis, five in number, had normal values. In 10 cases of active rheumatic fever included in Group II the average value was 0.48 mg per 100 c.c. with a range from 0.10 to 0.85 mg per 100 c.c., essentially the same as for the group as a whole.

The third group ("inadequate" vitamin C intake without infection) consists of 27 patients. In these the average serum ascorbic acid value was 0.48 mg with a range from 0.11 to 1.26 mg per 100 c.c.

The fourth group ("inadequate" vitamin C intake with infection) consists of 29 patients. In these the average value was 0.47 mg of ascorbic acid per 100 c.c. with a range of from 0.21 to 0.91 mg per 100 c.c., essentially the same as for Group III. (Figure 1)

Clinical signs of scurvy such as spongy, bleeding gums or spontaneous hemorrhages into the tissues were not observed in either Group I or Group II but were noted in ten patients in Group III and three patients in Group IV. There was no significant difference in the serum level of ascorbic acid between the patients with scurvy and those with equally poor diets without scurvy.

On encountering these results the question arises, "Could they not be due to lessened intake of vitamin C from lack of appetite or defective absorption associated with infectious disease?" In answer to this, it may be said that many of these patients were observed to be partaking of an adequate diet in the hospital, and in many the determination of serum ascorbic acid was done within a day or two of the onset of the disease before it would be expected that the effects of faulty absorption would become manifest.

A study of the vitamin C balance was carried out in four individuals with chronic infections—two patients with pulmonary tuberculosis, one with rheumatic fever, and one with lung abscess. Inasmuch as the observations in all four yielded essentially the same results only one case will be described in detail. T. W. was an elderly man with advanced pulmonary tuberculosis, who weighed 50 kilograms. Previous to entry to the hospital he had been

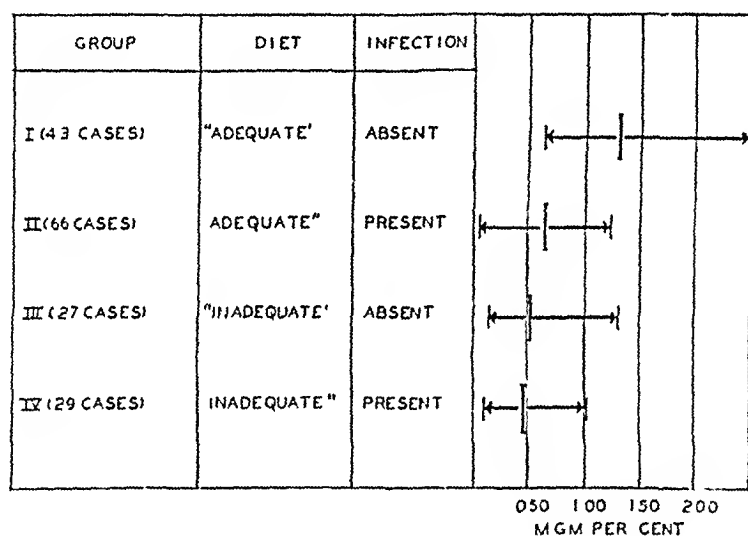


FIG. 1. Average serum ascorbic acid and range of values in various conditions

on a diet containing raw fruit or cabbage several times a week. His clinical condition remained essentially unchanged throughout the course of the observations. During his stay in the hospital he was kept on a basal diet which contained no fresh fruit, tomato or cabbage, in other words, it was moderately low but not completely lacking in vitamin C. On admission the serum ascorbic acid was 0.30 mg per 100 cc while the average total daily excretion into the urine was 3 mg, a very low value. These figures showed no essential change over a control period of three weeks. During the succeeding 10 days he was given on separate occasions one intravenous dose and two oral doses of one gram each of ascorbic acid. These large single doses of ascorbic acid were followed during the first 24 hours by an increased excretion of the vitamin in the urine amounting to 254 mg after the intravenous injection, and 21 and 71 mg, respectively, after the oral administrations. During the second 24 hours on each occasion the urinary

excretion fell to its previous low values. At the end of this period the plasma ascorbic acid had risen to 0.95 mg per 100 c.c. He was then given 500 mg of ascorbic acid by mouth daily for four weeks. The response to this amount was shown by a prompt rise in the plasma ascorbic acid to 1.31 mg per 100 c.c., accompanied by a marked increase in the urinary excretion to from 200 to 300 mg per day. Ascorbic acid administration was then discontinued for four weeks and there was a rapid fall in the plasma ascorbic acid to its preexisting low level. At this point increasing doses of ascorbic acid were given by mouth beginning with 100 mg per day for 13 days, then 200 mg per day for 17 days and finally 300 mg per day. It was not until the latter dosage had been instituted for several days that the serum ascorbic acid level and the urinary excretion of the vitamin rose to normal values (figure 2).

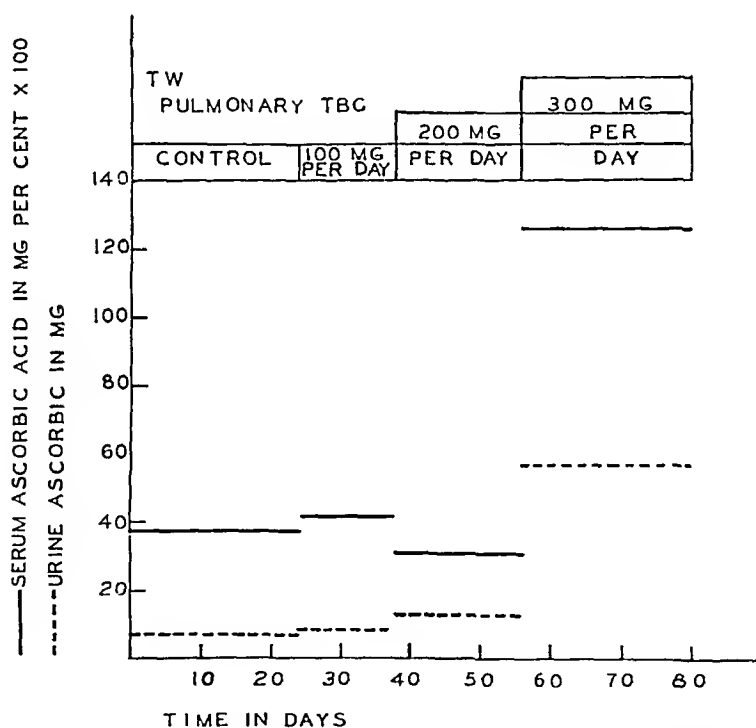


FIG. 2. The effect of oral administration of ascorbic acid on the serum values and urinary excretion of this substance in a patient with pulmonary tuberculosis.

DISCUSSION

The above experiment indicates that this patient who had active tuberculosis required more than 200 mg of ascorbic acid per day to keep his plasma level and urinary secretion of the vitamin at normal levels. This may be compared to the figures of van Eckelen²³ and of Heinemann²⁴ who found that the daily requirements of a normal adult weighing 70 kg are about 60 mg.

SUMMARY

The serum ascorbic acid has been estimated in a group of normal individuals, in patients with vitamin C deficiency, and in patients with infectious diseases

The serum ascorbic acid levels in patients with infections are usually well below the values seen in normal individuals and often reach figures encountered in manifest clinical scurvy

The amount of vitamin C in the diet necessary to bring the serum level and the urinary output to normal values in the presence of infection is far greater than the normal requirements

The effect of rheumatic fever on the vitamin C metabolism appears to be the same as that of other infectious diseases

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THE EFFECTS OF LARGE DOSES OF BENZEDRINE SULPHATE ON THE ALBINO RAT FUNCTIONAL AND TISSUE CHANGES

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Of the synthetic preparations of the epinephrine group, benzedrine (phenylisopropylamine) is in some respects more efficient than epinephrine and ephedrine, and also has additional therapeutic effects. As a sympathetic stimulant it produces mydriasis and piloerection (Alles¹, Prinzmetal and Bloomberg², Myerson, Loman and Dameshek³). It raises both blood and spinal fluid pressure, the rise being maintained for a longer period than after injection of the other two drugs (Alles¹, Piness, Miller and Alles⁴, Haitung and Munch⁵, Tainter⁶, Myerson, Loman and Dameshek³). Like these drugs, it increases the number of erythrocytes and leukocytes in the blood, and to a lesser extent the hemoglobin and the corpuscular volume (Myerson, Loman and Dameshek³). Applied to the mucous membranes of the nose, Eustachian tube or middle ear, benzedrine has a marked decongesting effect (Bertolet⁶, Bryne⁶, Scarano⁶, Wood⁶). In addition, it has been found to diminish the sense of fatigue, to prevent sleep, and to be of therapeutic value in the narcolepsies and allied conditions (Prinzmetal and Bloomberg²). Finally, it has been shown to lessen or abolish spastic manifestations of the gastrointestinal tract within a few minutes (Myerson and Ritvo⁷).

Most of these studies have been on clinical material, those on animals were not continued over long periods and did not include postmortem studies which might throw light on possible toxic effects.

It seemed desirable, therefore, to undertake studies on rats which would disclose signs of toxicity when benzedrine in hypertherapeutic amounts was given over long periods, and also establish the postmortem changes following lethal doses.

METHODS

For these experiments, 171 albino rats, weighing from 50 to 385 grams, were used, 145 rats were injected subcutaneously with benzedrine sulphate which had been dissolved in saline solution and sterilized by heat. The amount of benzedrine given by single injections varied from 1 to 500 mg per kilo of rat weight. Injections, with but few exceptions, were made on

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the first, fourth and sixth days and thereafter daily—six days a week—in one group for one and one-half weeks, in another for three weeks, in another for six weeks. Surviving rats were sacrificed and immediately autopsied 24 hours after the last injection, except in the case of one lot that was used to study the effect of increasing doses.

Of the remaining 26 rats, which served as controls, nine were injected with 0.5 to 2.0 c.c. of saline, while 17 received no injections.

To estimate functional changes, we observed the general behavior of the rats, the weight curve, the blood picture, and the blood urea. The blood picture was determined from a drop of blood from an incision in the dorsal surface of the tail. To avoid a possible anemia from loss of blood, we made only two to four counts on each rat of the number of the red and white cells and differential counts, according to standard routine. The blood urea was determined from blood collected after the animals had been decapitated. For these determinations we are indebted to Dr. W. G. Karr, of this University, who used the method of Folin and Wu.

For the morphological study, pieces of liver, kidneys, adrenals, heart, aorta, intestine, spleen, lungs and brain were fixed in alcohol, formalin and Zenker-formalin. The sections were stained with hematoxylin-eosin, Azur II-eosin, Best's carmine and Sudan III. In most instances stains for calcium and iron were also made.

RESULTS

1 *Lethal Dose* The lethal dose was determined first, since it should also show toxic effects, if there were any, especially with high sublethal doses. The results of these studies are given in table 1. Since heavier (older) rats

TABLE I
Lethal Dose of Benzedrine in Different Weight Groups

Dosage mg./1000 grams	Weight 50 to 95 grams				Weight 100 to 195 grams				Weight 210 to 385 grams			
	No. of rats	Average weight (grams)	Number dead after first injection	Number dead after fifth injection	No. of rats	Average weight (grams)	Number dead after first injection	Number dead after fifth injection	No. of rats	Average weight (grams)	Number dead after first injection	Number dead after fifth injection
20	3	88	0	0	13	140	0	1†(8)				
25					4	133	0	1*(25)	4	268	0	0
30	2	90	0	0	7	148	2†(29)	2†(20)	5	316	2(40)	3(60)
35	1	90	0	0	6	136	1†(17)	1†(17)	1	320	0	1(100)
40	4	80	0	0	9	150	1(11)	2(22)	2	243	2(100)	2(100)
50					11	135	5(45)	7(64)				
60	1	80	0	0	7	161	4(57)	5(71)				
80	3	77	0	0	5	119	4(80)	4(80)				
100	6	76	1†(17)	2†(33)	5	117	5(100)	5(100)				
150	4	81	1(25)	1(25)	3	130	3(100)	3(100)				
200	4	85	2(50)	4(100)	3	133	2(67)	2(67)				
300	2	75	2(100)	2(100)								
400	2	88	2(100)	2(100)								

Figures in parentheses = percentage dead

* In this rat death was due to paratyphoid

† In these rats the cause of death could not be ascertained, because they were found to be eaten up or completely autolyzed

‡ In one of these rats death was due to pneumonia, whereas the other apparently died from benzedrine

regularly died from much smaller doses per kilo than lighter (younger) ones, the results are presented in three groups: the first comprising animals weighing 50 to 95 grams, the second, 100 to 195 grams, and the third, 210 to 385 grams.

If we consider as the minimum lethal dose one which kills half or more of the animals injected, we find that for rats weighing 50 to 95 grams, this dose is about 200 mg per kilo, for rats weighing 100 to 195 grams, 50 to 60 per kilo, and for rats weighing 210 to 385 grams, 30 to 40 per kilo. Of the 10 rats which died with smaller doses, six could be examined histologically. Of these, one showed a heavy paratyphoid infection, and one an extensive purulent pneumonia, whereas the other four apparently died from benzedrine.

In general, the rats died the more quickly the larger the dose given. This holds true for all three weight groups.

The question why seven rats (excluding those that had complicating infections) died only after several injections cannot be answered with certainty. But since four of them received the second injection three days after the first only, and the third two days after the second, and since these rats died only after they had received two to three *daily* injections, it might very well be that the drug was not eliminated completely during the 24 hours between the injections, or that they had not recovered completely before they were again injected. As far as we can learn, there is as yet no knowledge of the method and rate of elimination of the drug or of its destruction within the body. That its action lasted more than eight hours can be deduced from the fact that treated rats ate less the next night (12 to 24 hours after the injection) and that rats which received large doses frequently were found to be still excited 24 hours after the injection.

As to tolerance, we have definite evidence that it was increased by repeated injections, in animals which survived the first four or five. If we injected 20 to 150 mg per kilo for four to 21 days and increased doses thereafter until the animals died, we found (table 2) that in most animals the dose had to be increased to 300 to 500 mg per kilo to have a lethal effect.

In regard to the minimum lethal dose, our figures are considerably higher than the 25 mg per kilo reported by Hartung and Munch⁵ for benzedrine hydrochloride. While there should be little difference in the action of equal doses of the two salts, 100 mg of the hydrochloride being equivalent to 107 mg of the sulphate, the discrepancy may be explained by the different weights (ages) of the animals used. In our series only the third group consisted of adult or almost adult rats, while those of Hartung and Munch may all have been fully adult or even aged.

2 General Behavior. As soon as 15 minutes after the first injection the rats began to run around excessively, to gnaw at the iron wires of their cages, and, when a dish of water was in the cage, to splash in it. The pupils were very wide and with larger doses did not react to light. The degree

and the course of this excitement varied with the dose of benzedrine. Rats receiving 1 to 5 mg per kilo of weight were not at all or moderately excited after two to three hours, almost calm after four hours, and quite calm after six to seven hours, rats receiving 5 to 20 mg were much excited after two and a half hours, moderately excited after four hours, and calm to moderately excited after six to seven hours, rats receiving 20 to 80 mg were very much excited after two and a half to three hours and after four hours, and moderately to much excited after six to seven hours. Rats which received 30 mg or more showed very queer movements, they ran backwards or in circles, even had difficulty in walking, often sat up on their hind legs, pawing the air and falling over backward. Many rats developed diarrhea.

TABLE II
Lethal Dose of Benzedrine if Applied Daily in Increasing Doses (27 Rats)

No of rat	Weight (grams)	Benzedrine mg /1000 grams	Total mg per kilo given	Total no of doses	Found dead hrs after last injection
18/1	75	100(5) 150(1) 200(1) 300(1)	1150	8	1
18/2	80	100(5) 150(1) 200(1) 300(1) 400(1)	1550	9	4 ¹
18/3	80	150(5), 200(1), 300(1) 400(1)	1650	8	1 ¹
37	85	150(4) 200(1) 300(1)	1100	6	1
21	90	30(5), 80(1) 100(1) 150(1) 200(1) 300(1)	930	10	3
22	95	40(5), 80(1) 100(1) 150(1) 200(1) 300(1) 400(1)	1430	11	2
8/5	110	20(21) 80(1) 100(1)	600	23	6
20/6	110	35(4) 40(1), 50(1) 60(1) 80(1) 100(1) 150(1) 200(1) 300(1)	1120	12	1
7/7	115	20(21) 60(1), 80(1) 100(1)	660	24	3 ¹
20/9	115	35(4) 40(1), 50(1) 60(1) 80(1) 100(1) 150(1) 200(1) 300(1) 400(1) 500(1)	1820	14	3
20/8	115	40(4) 50(1) 60(1) 80(1) 100(1) 150(1) 200(1) 300(1) 400(1)	1500	12	2
8/7	120	20(21) 80(1) 100(1)	600	23	4
8/3	120	20(21) 100(1)	520	22	1
20/7	125	40(4) 50(1), 60(1), 80(1) 100(1) 150(1) 200(1) 300(1) 400(1)	1500	12	2
24	155	30(5) 100(2) 150(1) 200(1)	600	9	5
17/5	165	30(5), 40(1) 50(1) 60(1) 80(1) 100(1)	480	10	3-47
17/6	165	30(5) 40(1) 50(1) 60(1) 80(1)	380	9	7
20/5	170	35(4) 40(1)	180	5	3 ¹
20/1	185	35(4) 40(1) 50(1) 60(1) 80(1) 100(1) 150(1) 200(1) 300(1) 400(1)	1520	13	2
20/3	190	40(4) 50(1) 60(1) 80(1) 100(1) 150(1) 200(1) 300(1) 400(1) 500(1)	2000	13	1 ¹
7/6	195	20(21) 60(1) 80(1) 100(1) 150(1) 200(1) 300(1) 400(1)	1710	28	1
16/5	210	25(4) 30(1) 35(1), 40(1) 60(1) 80(1) 100(1) 150(1) 200(1) 300(1) 400(1)	1495	14	2
16/6	210	25(4) 30(1) 35(1) 40(1) 60(1) 80(1) 100(1) 150(1)	995	11	2
21/3	290	30(4) 35(1) 40(1) 50(1) 60(1) 80(1) 100(1) 150(1) 200(1) 300(1)	1135	13	2
21/2	310	25(4) 30(1) 35(1) 40(1) 50(1) 60(1) 80(2) 150(1) 200(1), 300(1) 400(1)	1525	15	2 ¹
16/3	320	30(4) 35(1) 40(1) 50(1) 60(1) 80(1) 100(1) 150(1) 200(1) 300(1)	1135	13	6
21/4	340	25(4) 30(1) 35(1) 40(1) 50(1) 60(1) 80(1) 100(1) 150(1)	645	12	6

Figures in parentheses = number of injections given at each dosage level

After repeated injections similar observations were made. After the third or fourth injection, it was also noted that the rats which received 30 mg or more fought a great deal. In two rats receiving 10 and 30 mg per day a very unusual phenomenon was observed. Three hours after the second injection they were found to gnaw their own thoracic skin.

After injections had been continued for more than one to two weeks, rats did not react as strongly as they did after the first injections. They were less excited, and for shorter periods.

A rat about to die from benzedrine lay down and "faded away". Al-

though the death of practically all the rats was observed, nothing approaching tremors or convulsions, as reported by Alles¹ for guinea-pigs, was observed at any time

3 Weight Of the 55 rats the weights of which have been followed, 30 were discarded when found to be sick from spontaneous diseases. Of the 25 remaining rats, 16 have been followed for three to six weeks. The weight curves of these rats are given in figures 1 to 3, together with normal weight curves, as given by Donaldson and Ferry⁸. Comparison shows that at first most rats stopped growing for three to four weeks, after which most of those receiving less than 20 mg. per day grew again, while those receiving higher doses failed to do so. It can also be seen that younger rats (figure 1) did better than older ones (figure 2).

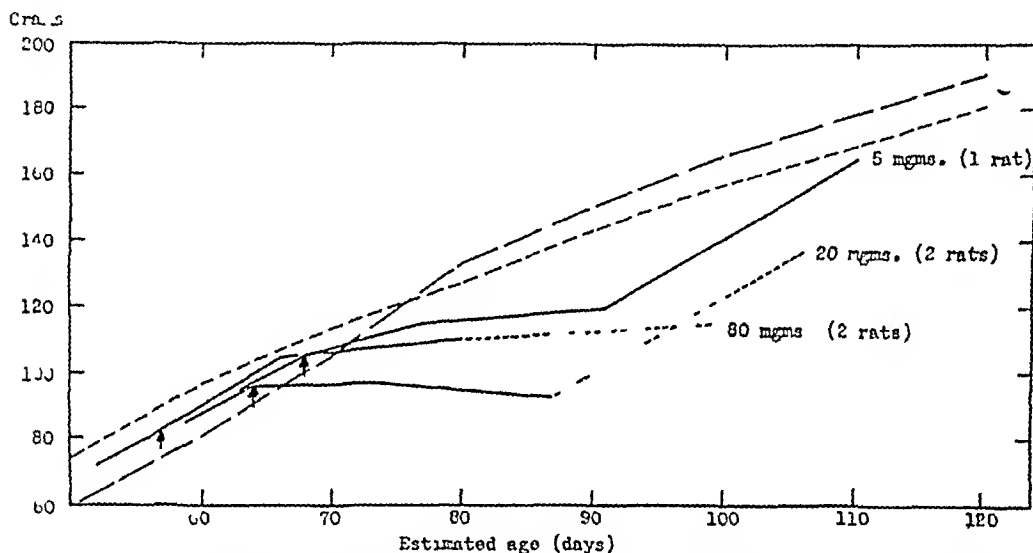


FIG 1 Transient inhibition of growth by daily injections of benzedrine ——— Experimental rats (male, weight group 50 to 95 grams), the dotted continuation gives the curve of the one rat that survived ——— Normal weight curve based on data of Donaldson, Dunn and Watson - - - - Normal weight curve based on data of Ferry An arrow indicates when benzedrine dosage was started

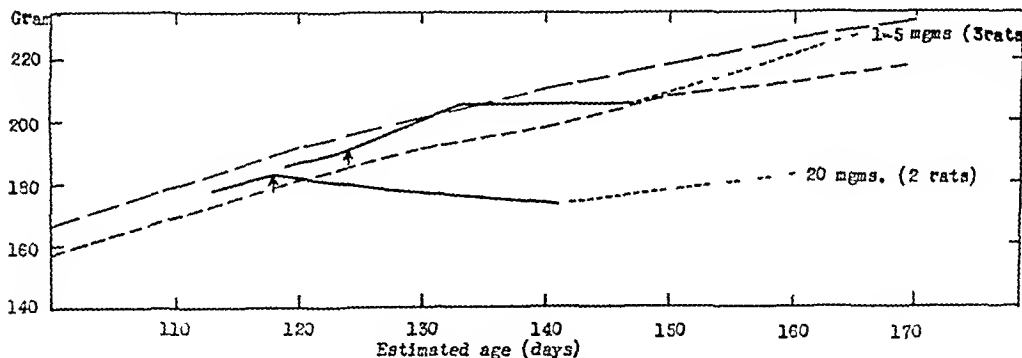


FIG 2 Transient inhibition of growth by daily injections of benzedrine ——— experimental rats (male, weight group 150 to 205 gm), ———, - - - -, and arrow, as in figure 1

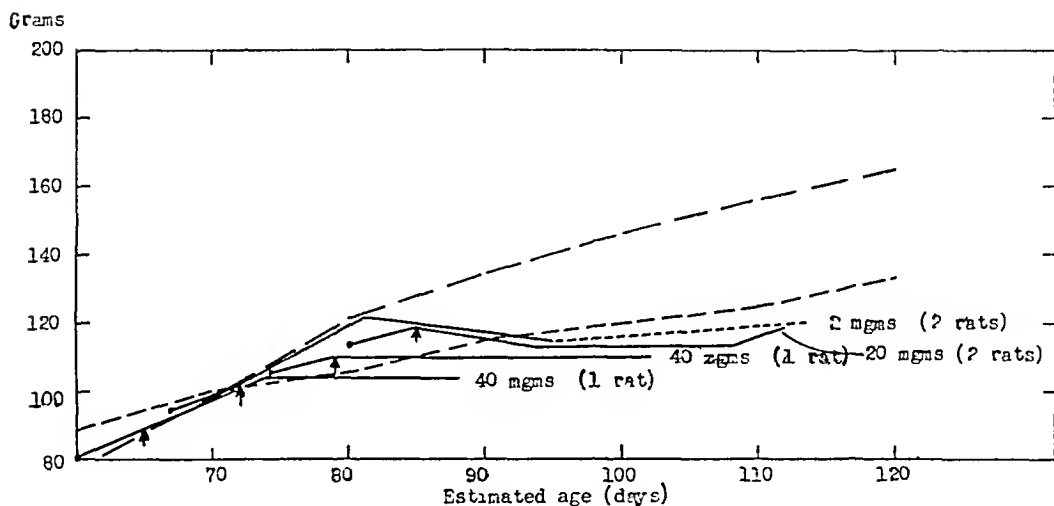


FIG 3 Transient inhibition of growth by daily injections of benzedrine ——— experimental rats (female, weight groups 50 to 95 and 100 to 130 gm), ———, ———, and arrow, as in figure 1

Weight changes and food intake of the remaining nine rats (four treated with benzedrine, and five controls) are given in table 3. They correspond to the previous figures. In addition, they show that the daily food intake, as measured by weighing the amount of food (Purina Dog Chow) given in the morning and left on the next morning, was conspicuously lowered in

TABLE III
Changes of Weight and Food Intake During Nine Days of Treatment

No of rats	Original weight (grams)	Treatment	Average weight increase (per cent)	Average daily food intake (grams)
<i>Control Group</i>				
2	75-100	None	+51	} 17.5
2	80-100	1 c c saline	+58	
1	155	1 c c saline	+16	
<i>Benzedrine</i>				
2	85-100	50-100 mg	+16	} 13.7
2	155-165	25 mg	+ 3	

the treated animals as compared with the controls. This finding indicates that decreased food intake is a factor in the inhibition of growth.

4 *Red and White Blood Cells* The changes in the number of erythrocytes and leukocytes in the blood have been followed in 36 treated and six control rats. In all instances the determinations were made 24 hours after the last injection. As 21 of the treated animals and four of the controls had to be excluded on account of the presence of spontaneous disease at autopsy, the counts on 15 treated and two control rats only were available.

The changes in the number of erythrocytes in our treated rats are presented in figure 4. For comparison, the normal increase in the number of erythrocytes (which in our rats amounted to 0.22 millions of erythrocytes per 10 grams of weight increase) has been given. We found that, with the exception of two rats which received 1 mg benzedrine daily, all our rats responded with an erythrocytosis. Whereas in the rats receiving 2 to 5 mg of benzedrine daily this increase amounted to 40 per cent on the sixteenth day, in those receiving 20 mg, it amounted to about 50 per cent after 16 to 23 days, and in those receiving 40 to 80 mg to 55 per cent, after 43 days, i.e., on the last day of this experiment.

The individual leukocyte counts were not as uniform as the erythrocyte counts, and there were no distinct differences in the animals treated with different doses. On the average, at first both granulocytes and lymphocytes

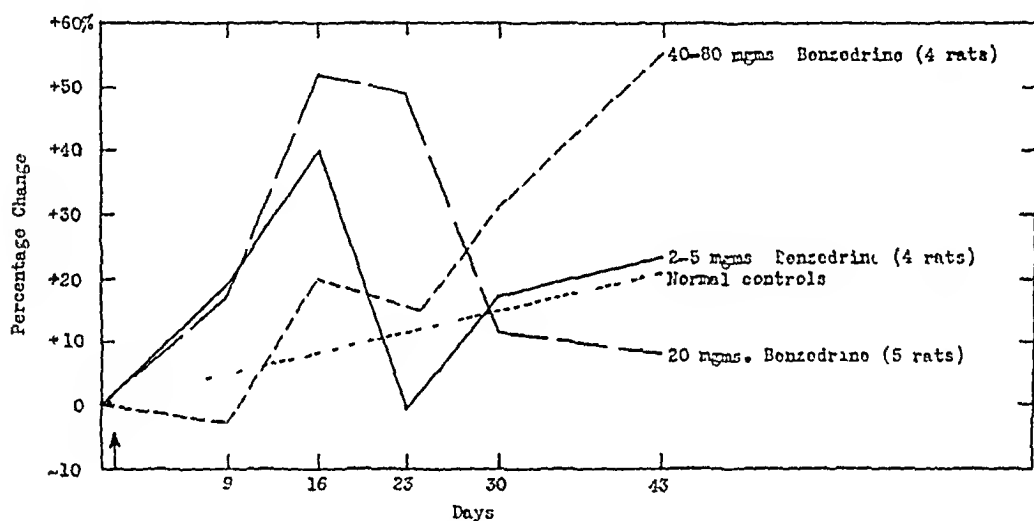


FIG 4 The percentage changes in the number of erythrocytes after 2 to 5, 20, and 40 to 80 mg of benzedrine daily. An arrow shows when benzedrine dosage was started.

rose considerably. After 16 days there was a marked preponderance of granulocytes, and after 23 days of lymphocytes. After 30 days, however, both granulocytes and lymphocytes had returned to normal in spite of the daily dosage being continued (figure 5).

These findings correspond in general to those of Myerson, Loman and Dameshek in men, as well as to those which have been obtained with epinephrine and ephedrine in a variety of animals. As to the mechanism producing these changes no new information was obtained. It may be mentioned that in a few animals tested the icterus index was normal.

5 Blood Urea The blood urea has been determined in 33 treated and five control rats, 28 to 29 hours after the last injection. In all the rats receiving 1 to 20 mg of benzedrine daily for three or six weeks, or 30 to 200 mg for one and a half weeks (with the exception of three rats which had

an extensive spontaneous disease) the blood urea was found to be within normal limits 17 to 26 mg per cent (average 23 mg per cent), as compared with 20 to 24 mg per cent (average 23 mg per cent) in our controls. In the four rats which received 40 to 80 mg daily for three or six weeks it was found to amount to 34, 50, 52 and $70 \pm$ mg per cent. Since two of these rats showed no spontaneous disease whatsoever, and another had one tapeworm only, it may be assumed that in these animals the rise in blood urea was due to the injections.

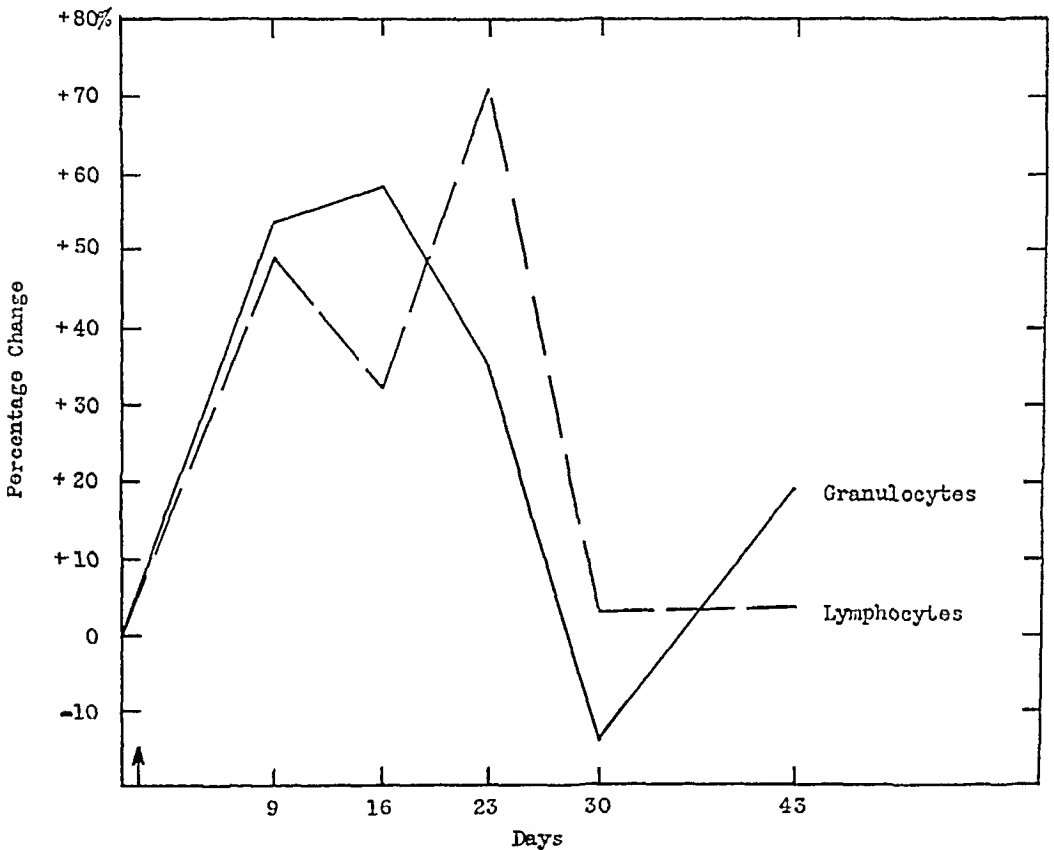


FIG 5 The percentage changes in the number of granulocytes and lymphocytes after 1 to 80 mg of benzedrine daily. An arrow indicates when benzedrine dosage was begun.

6 Gross Pathology In the animals which were killed by the benzedrine, various lesions were found. Frequent changes were marked and sharply delimited constrictions of the small intestine, air and fluid in stomach and intestine, congestion of the liver, either contraction or congestion of the spleen, and subpleural hemorrhages in the lungs. As the changes in the amount of blood in spleen and liver appear to be of special interest, we have tried to analyze them (table 4). Correlating these changes with the time which elapsed between injection and death, we find that the congestion of the liver was most marked in the animals which died after two hours,

TABLE IV

Amount of Blood in Liver and Spleen in Rats Which Died from Benzedrine, as Compared with the Time the Rats Survived

Died hrs after last injection	No of rats	Average dose of benzedrine (mg.)	Average weight (grams)	No. of rats showing different amounts of blood in					
				Liver			Spleen		
				Normal	Slight incr	Great incr	Decr	Normal	Incr
—	10	0	112.5	10	0	0	1	9	0
1-1	4	300	124	1	2	1	2	0	2
1-2	7	179	121	0	0	7	4	2	1
3-5	13	167	130	0	7	6	6	1	6
6-24	3	57	155	1	1	1	1	1	1

less marked after three to five hours, and less marked still after six to 24 hours, whereas the changes in the spleen showed no relationship to the time of death after injection. However, comparison with the dosage of benzedrine (table 5) shows that most of the animals which received 30 to 100 mg. had congested spleens, and those which received 150 to 400 mg. contracted spleens, whereas the livers showed no relationship. From these findings we may conclude that the contraction of the spleen was due to the action

TABLE V

Amount of Blood in Liver and Spleen (Percentage Incidence) in Rats Which Died from Benzedrine, as Compared with the Dose Given

Dose of benzedrine (mg.)	No. of rats	Average weight (grams)	Died hrs after last injection (average)	Amount of Blood in					
				Spleen			Liver		
				Decr	Normal	Incr	Normal	Slight incr	Great incr
0	10	112.5	—	10*	90	0	100	0	0
30-100	12	147.5	4.4-5.6	25	17	58	8	42	50
150-400	15	115	2.5	67	13	20	7	27	66

* Percentage of rats

of benzedrine, whereas the congestion of the liver and spleen was merely a sign of the circulatory insufficiency that existed just before death. The fact that the spleens of the rats which received smaller doses of benzedrine were congested in most cases may be explained by the assumption that in these animals the effect of circulatory failure was greater than that of the benzedrine, whereas in the animals with larger doses the effect of the drug

predominated. As the surviving animals which were killed 24 hours after the last injection showed no lesions attributable to the treatment, they are omitted here.

7 Histology A Necroses With the exception of 11 rats which were eaten up or in an advanced state of autolysis, all rats were carefully examined histologically. In no instance, not even in animals which for six weeks received 40 to 80 mg of benzedrine daily, were we able to find areas of degeneration, necroses or calcification in the myocardium, in the arteries or in the muscular coat of the intestine, as described in chronic adrientalism (Petri⁹). Nor did we find any "parenchymatous degeneration" of the kidneys as described by Chen¹⁰ after administration of ephedrine. Many slides, to be sure, showed vacuolization of the tubular epithelial cells when fixed in alcohol and stained with hematoxylin-eosin, or a fibrinoid granulation of these cells when fixed in Zenker-formalin and stained with Azur II. Although this observation is of interest pathologically and, as far as we know, has not been previously reported, it is not relevant to the present study, as it was obviously dependent upon spontaneous diseases of the rats, especially upon paratyphoid and purulent infections (see table 6).

TABLE VI

Tubular Degeneration of Kidneys as Compared with Benzedrine Injections and Spontaneous Disease

	No of animals	Tubular degeneration			
		0	+	++	+++
Controls (healthy)	15	9	2	3	1
Benzedrine (healthy)					
1-25 mg	13	11	1	0	1
30-50 mg	15	13	1	1	0
60-100 mg	11	11	0	0	0
150-400 mg	13	13	0	0	0
Paratyphoid					
Mild	12	5	6	1	0
Medium	9	0	2	6	1
Heavy	10	0	1	2	7
Purulent bronchopneumonia, appendicitis, middle ear infection, etc	7	3	1	2	1

The only changes which could be connected with the benzedrine injections were necroses in liver, spleen and kidneys, and changes in the sugar and fat depots. Necroses in liver, spleen and kidneys were found only in rats which died from benzedrine. Rats which survived the injections never showed any necroses or scars when killed later. If we compare the occurrence of necroses with the dosage of benzedrine (table 7), we find that only those rats which died from 30 to 100 mg of benzedrine per kilo exhibited necroses, whereas those which received higher doses did not. A similar

TABLE VII
Liver Necroses as Compared with the Dose of Benzedrine Given (Single Doses)

Dose of benzedrine (mg.)	No. of rats	Liver necroses			
		None	Slight	Medium	Extensive
30-40	9	1	1	2	5
50-60	11	2	3	4	2
80-100	6	2	2	1	1
150-200	5	5	0	0	0
200-400	6	6	0	0	0

result was obtained when the animals were treated with increasing doses (table 8). As to the cause of this phenomenon we have no explanation at present.

TABLE VIII
Liver Necroses as Compared with the Dose of Benzedrine Given (Increasing Doses)

Highest dose of benzedrine given (mg.)	No. of rats	Liver necroses			
		None	Slight	Medium	Extensive
40-80	2	0	0	1	1
100-150	7	1	3	2	1
200-400	18	18	0	0	0

B. Carbohydrate and Fat Changes Changes in the sugar and fat deposits on the other hand were found in both groups of rats. If rats, after one and a half weeks of treatment, were killed by ether one day after the last injection, and if they had no spontaneous diseases, the glycogen content of the liver as well as of the para-aortal, para-renal, para-adrenal and mesenteric fat tissue, as seen by Best's carmine stain, was found to be increased in those rats receiving more than 25 mg., whereas the fat content of these organs was found in Sudan III stained slides to be decreased (table 9). Similar results were obtained by a chemical analysis for which we are indebted to Dr. Evans of the Cox Institute (table 10). Since fat tissue could not be obtained in an amount large enough to permit such an analysis, this was not studied. Instead, the heart glycogen was determined, this, however, appeared to be within the normal limits (table 10).

In the rats killed after three or six weeks of treatment the glycogen could not be determined correctly, because the time between decapitation and fixation of tissues was long enough to have permitted loss of glycogen. The fat, however, could be estimated, since its values do not change as quickly after death as those of glycogen. The results of this estimation are in accord with the findings after one and one-half weeks (table 11).

TABLE IX

Changes in Glycogen and Fat after One and a Half Weeks of Treatment with Benzedrine
Glycogen

Treatment	No of rats	Liver				Fat tissue			
		None	Slight amt	Mod amt	Great amt	None	Slight amt	Mod amt	Great amt
Controls									
None	15	1	3	7	4	12	2	1	0
Saline	3	0	1	2	0	3	0	0	0
Benzedrine mg									
2	1	0	1	0	0	1	0	0	0
25	3	0	0	3	0	1	2	0	0
30-50	9	0	0	3	6	1	3	2	3
60-100	6	0	0	2	3	1	1	2	2
150-200	2	0	0	0	2	1	1	0	0

Fat

Controls									
None	13	1	2	4	6	0	0	2	11
Saline	—	—	—	—	—	—	—	—	—
Benzedrine mg									
2	1	0	0	1	0	0	0	0	1
25	1	0	0	1	0	0	0	0	1
30-50	8	4	4	0	0	0	0	4	4
60-100	5	4	1	0	0	0	0	4	1
150-200	2	2	0	0	0	0	0	2	0

TABLE X

Changes in Glycogen and Fat after One and a Half Weeks of Treatment with Benzedrine
(Chemical Analysis)

Treatment	Rat No	Weight gm	Glycogen per cent		Fat per cent liver
			Liver	Heart	
Average (6 Controls, Dr Evans)	—	—	2.08	0.414	—
Our controls					
None	15/2	125	1.37	0.424	3.87
"	15/4	140	1.60	0.437	—
Saline	15/1	130	1.47	0.386	3.35
"	15/3	155	2.48	0.399	3.85
"	15/5	180	2.20	0.382	—
Average		146	1.87	0.403	3.69
Benzedrine					
100 mg	14/1	95	2.84	0.258	2.65
50 "	14/4	120	2.63	0.325	3.02
25 "	14/5	160	2.19	0.495	2.95
25 "	14/6	170	3.02	0.700	—
Average		136	2.67	0.445	2.87

TABLE XI
Changes in Fat after Three and Six Weeks of Treatment with Benzedrine

Treatment	No of rats	Liver				Fat tissue			
		None	Slight amt	Mod amt	Great amt	None	Slight amt	Mod amt	Great amt
Controls									
None	13	1	2	4	6	0	0	2	11
Saline	2	0	0	1	1	0	0	0	2
Benzedrine mg									
1-5	6	1	1	2	2	0	0	3	3
10-20	5	1	3	1	0	0	0	2	3
40-80	3	3	0	0	0	0	0	3	0

In addition, they seem to indicate, that after three or six weeks' treatment the decrease in fat is more pronounced still, and that it is apparent already in animals which received less than 25 mg of benzedrine per day.

In the rats dying after one or two injections of benzedrine, no glycogen was found in liver or fat tissue, if the animals died after six to 11 increasing doses, however, invariably an increase in glycogen was noted. The fat content of the liver was not changed in the first group, whereas in the latter group we found no fat whatsoever in the liver and a markedly decreased amount in the fat tissue.

Concerning the significance of these findings, it may be mentioned that after epinephrine the liver glycogen is also first decreased and then increased (Cori¹¹). As to the mechanism involved in these changes we have no new suggestions to offer.

COMMENT

The question whether benzedrine if given in large doses has toxic effects or not is difficult to answer. We have found that in experimental doses (which it should be remembered are from five to several hundred times the human therapeutic dose) it may cause excitement, diarrhea, mydriasis, transient inhibition of weight increase in young rats, erythrocytosis, leukocytosis and changes in the glycogen-fat content of liver and fat tissue. Most of these changes were temporary, some for hours only (excitement, mydriasis, diarrhea), some for weeks (erythrocytosis, leukocytosis, inhibition of weight increase). The changes in the glycogen-fat content of liver and fat tissue appeared to be permanent during the time that benzedrine was given.

It was also found that the lethal dose was proportionately higher for small (young) rats than for large (old) ones, and that large doses caused more marked and longer lasting changes in both large and small rats than did small ones. For instance, most of the animals receiving 25 mg of benzedrine or more were much more affected than those receiving smaller doses, they were the only ones which showed, (1) queer body movements

after each injection, (2) a definite increase in glycogen and a definite decrease in fat in liver and fat tissue, (3) a persisting failure to increase in weight, and (4) a persisting increase in the number of erythrocytes in the blood

Whether or not these changes should be looked upon as toxic, appears to be a matter of definition, for if we should call those doses toxic which merely produce transient, undesirable functional variations, then such relatively small doses as 2 to 5 mg of benzedrine per kilo would be regarded as toxic. But if we regard as toxic only those doses which produce actual lesions, i.e., pathologic tissue changes, then the toxic dose appears to be practically the same as the lethal dose. This in rats under 100 gm weight was found to be about 200 mg per kilo, in rats of 100 to 195 gm, 50 to 60 mg, and in rats over 200 gm, 30 to 35 mg.

The evidence is clear cut that smaller (younger) rats are more resistant to equivalent doses of benzedrine than larger ones. The reason for this, however, is quite obscure to us, especially as we know of no studies that demonstrate the fate of benzedrine in the body. Whether the younger animal can break down or excrete the substance more rapidly or completely than the older, or whether the younger tissues are intrinsically more resistant to the drug, or the circulation more efficient in the young, are questions that remain unanswered.

SUMMARY

The functional and structural changes produced by the subcutaneous injection of benzedrine sulphate into rats were studied in widely varying doses over varying periods. One hundred and seventy-one albino rats, weighing from 50 to 385 gm, were used. One hundred and forty-five were injected subcutaneously with doses of 1 to 500 mg per kilo from 1½ to 6 weeks.

The minimum lethal dose decreased with the weight (age) of the rats. In animals of 50 to 95 gm it amounted to 200 mg, in rats of 100 to 195 gm, to 50 to 60 mg, in rats of 210 to 385 gm, to 30 to 35 mg per kilo. After repeated injections an increased tolerance was noted.

If 2 to 5 mg or more were given, the rats showed excitement, diarrhea, mydriasis, transient inhibition of weight increase, erythrocytosis, leukocytosis and so on. With 25 mg and more they showed an increase in glycogen and a decrease in fat in liver and fat tissue.

In rats which died from the drug, frequent changes were observed. Constrictions of the small intestines, congestion of the liver, either marked constriction or congestion of the spleen and subpleural hemorrhages in the lungs. Rats which died from 30 to 100 mg of benzedrine showed necroses in liver, spleen and kidneys, whereas those which died from higher doses did not. Lesions in the myocardium, arterial or intestinal walls, such as observed in chronic adrenalism, were not found. Rats killed after recovery from non-lethal doses showed no detectable lesions.

CONCLUSIONS

The minimum lethal dose of benzedrine sulphate given subcutaneously to rats is from a hundred to a thousand times per kilo the usual therapeutic dose given man orally

The greatest non-toxic dose, i.e., that which fails to produce transient variations, appears to be from 2 to 5 mg per kilo, in other words about 10 to 50 times per kilo the usual human therapeutic dose

The failure of repeated sublethal doses to produce detectable lesions in rats indicates that there should be a considerable margin of safety in the proper therapeutic use of the drug

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CASE REPORTS

GLOSSOPHARYNGEAL NEURALGIA DUE TO AN IMPACTED WISDOM TOOTH *

By DAVID RIESMAN, M D , Sc D , F A C P , *Philadelphia, Pennsylvania*

IN a recent article Hoover and Poppen¹ call renewed attention to the *douloureux* involving the glossopharyngeal nerve. They report two cases of their own and collect a number of others recorded in the literature. The pain is of the same nature as that of *douloureux* except that it is located at the base of the tongue and in the back of the throat instead of in the face.

Medical treatment is not very effective—it consists chiefly of the inhalations of from 15 to 30 drops of trichlorethylene three or four times a day. Such treatment frequently stops the pain but does not in any sense bring about a cure. In a number of cases, including one of Hoover and Poppen's, surgical treatment has been employed. In their opinion intracranial section of the ninth nerve in the posterior fossa, a formidable operation, is the procedure of choice.

I want to call attention to a cause of glossopharyngeal neuralgia which should it exist renders such an operation entirely unnecessary, nothing more being required than the extraction of an impacted wisdom tooth.

The first case concerns a man about 50 years of age who began to have violent pains in the throat on eating and speaking. He was obliged to lecture frequently and sometimes while lecturing he would be seized with such a spasm of pain that he thought he would become delirious. The pain would not last long but while it lasted the patient had to hold on to something for fear of falling in a faint. The pain was felt in the back of the throat, in the tonsillar region, and at the base of the tongue—never in the teeth. Throat specialists told him he had gout and ordered salicylates and iodides, but the treatment had not the slightest effect. A dentist declared the teeth normal except for an impacted wisdom tooth. Thinking that this tooth might be responsible for the frightful neuralgia, I insisted that the tooth be removed. It was extracted with difficulty by the late Dr. Matthew Crver, but from that time on the man has been entirely free from pain. The tooth itself was healthy.

The second patient was a man of 48 years who while in good health was suddenly seized with agonizing pain in the throat which unlike the pain in the first case was not paroxysmal but was more or less constant. For 10 days he had hardly had any sleep despite a variety of strong sedatives. A dentist had declared his teeth to be normal. The case was so similar to the other that I suspected an impacted wisdom tooth. The roentgen-ray films showed such a tooth. It was extracted and the pain disappeared immediately and never returned. Neither of the two patients had any toothache or connected the pain with his teeth.

On the basis of these two impressive experiences I would advise search for an impacted wisdom tooth in cases of glossopharyngeal neuralgia and if one is

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found, that it be extracted, regardless of a dentist's opinion to the contrary, before resorting to more radical measures

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MAJOR PSYCHOSIS IN UNDULANT FEVER *

By FRED E. ANGLE, M.D., and W. H. ALGIE, M.D., *Kansas City, Kansas*

MENTAL symptoms have frequently been observed during the course of undulant fever. In a study of 154 cases, we have encountered only one major psychosis. We found no reference to this condition as a complication of undulant fever in the American literature. Nouvilas¹ reported four cases from the Asylum of Navarre, Roger² collected 15 cases from the literature and reported three of his own. In a series of 200 cases, Cantaloube³ reported delirium in 12 and mental confusion in ten.

CASE REPORT

T. H., a white male business college student, aged 23, was admitted to the hospital January 8, 1936, in a state of violent catatonic excitement.

His illness had begun December 20, 1935, with a sore throat, chilly sensations, fever of 102° F, sweating, stiffness and soreness in the back of the neck. Two weeks later, as he continued to have fever from 100° F to 101° F and drenching sweats, he was sent to a hospital where it was found that his blood serum agglutinated *Br. abortus* in a dilution of 1:640. It was learned that he had been a habitual drinker of raw milk. His condition was diagnosed as undulant fever. After a short period of observation he was sent home. January 6, he was despondent, irritable, and, at times, mildly delirious. On this date he was given 0.25 c.c. of *Br. abortus* vaccine intramuscularly. This was followed in a few hours by increased fever, chills, and a more severe delirium. The reaction subsided promptly but recurred the next day following the administration of 0.5 c.c. of the vaccine. He was mildly confused when seen in consultation January 8. It was decided that he should be sent to the hospital for observation. When the ambulance came for him, he became very excited, negativistic and violent.

The family history was entirely negative for mental disturbance.

He had never had a severe illness. He was intelligent and had never shown any psychopathic tendency.

Examination. He was six feet one inch tall and weighed 190 pounds. His axillary temperature was 103° F and his pulse rate was 120 per minute. Detailed physical examination was impossible on admission because of his violent activity but after large doses of sedatives, he became quiet enough to permit completion of the examination which revealed nothing but a moderate pharyngitis and a dry swollen tongue.

Laboratory examination. Hemoglobin 84 per cent (Sahli), red blood cells 5,700,000, white blood cells 8,150 with 63 per cent neutrophils, 34 per cent lymphocytes, and 3 per cent eosinophiles. The serum agglutinated *Br. abortus* in a dilution

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of 1 1280 Blood Wassermann and Kahn tests were negative Urine Specific gravity 1 009, albumin, negative, sugar, negative, microscopic examination, no cells or casts

He was very ill, during the first week his pulse ranged from 120 to 150 per minute and his rectal temperature from 104° to 105 8° F He perspired so profusely that he became dehydrated in spite of an increased oral intake and parenteral administration of fluids The latter part of the first week he developed a productive cough with râles in the right hilar region and base These signs disappeared in a few days While the fever was at its height a mild intention tremor of the hands was present The temperature reached its peak January 14, after which it fell gradually and by the end of the second week it was only 99 6° to 100° F There were no abnormal physical findings at this time No specific therapy was attempted after admission to the hospital

A lumbar puncture was made January 11, with the following findings Clear fluid, 18 cm of water pressure, no block, cell count 1, no increase in globulin, Wassermann negative and no decolorization of gold solutions Blood cultured the same day was negative a week later The intradermal test with *B abortus* vaccine applied the first week was strongly positive At the end of the second week the agglutination titer was still 1 1280

During the first two weeks, his mental state varied from catatonic excitement to stupor He had to be restrained constantly In the excited periods, he was violently hyperactive and very noisy He had both visual and auditory hallucinations to which he responded with obscene accusations and violent threats There were also absurd transient delusions, usually of a grandiose character Disorientation was complete for time and space and partial for persons At times he was rigid, negativistic, and mute He ate very little but took fluids well He urinated and defecated in bed Sedatives had little effect and he slept fitfully, less than five hours in each twenty-four

After the second week, he was less agitated, seldom rigid or mute but was unchanged otherwise The insomnia persisted Early in the fourth week his temperature again increased to 104° F and was accompanied by increased agitation but the temperature subsided to normal in a few days and the agitation decreased From this time there was little evidence of toxemia He ate well and slept fairly well He had lost more than 40 pounds during his illness Repeated neurological examinations revealed no evidence of any focal lesion of the brain or spinal cord Gradually, he became quieter and more tractable and was released from restraints During the latter part of March, he was allowed to be up in his room when supervised and allowed to go to the bathroom He continued to be hyperactive and hallucinated He was very destructive to his clothing and bedding and was frequently nude

April 9, he was transferred to the State Hospital for the Insane at Osawatomie There, he was given a therapeutic course of malaria as an empirical procedure From the early part of May, his mental condition cleared up rapidly and he was dismissed June 15, apparently normal

Since his return he has been seen frequently There has been no psychotic tendency He has regained his normal weight and strength For a time he continued his studies in the business college and reported normal progress At present he is working in a packing plant So far there has been no indication of a return of his undulant fever September 21, 1936, his agglutination titer was 1 10 complete, 1 40 partial and the opsono-phagocytic reaction marked

Note T H was contacted May 1, and found to be employed doing stenographic work There has been no return of his mental symptoms

Comment Although the early symptoms of psychosis had preceded the administration of the vaccine they developed much more rapidly following its

use The symptoms of general intoxication, likewise, were greatly intensified We were so impressed by this fact that we considered it unwise to continue the vaccine therapy The presence of a psychosis, we believed, should be added to the list of contra-indications to the use of vaccine already reported ⁴

The mental symptoms which occur as a result of a toxic or infectious state may develop into typical psychiatric patterns ⁵ Such a case was reported by Nouvilas ¹ in which the admission diagnosis was schizophrenia, but before the patient left the hospital the diagnosis was revised to acute infectious psychosis Our case has many features of catatonic schizophrenia, but due to the rapid evolution with complete recovery and the absence of any previous abnormal mental trends, we believe the condition was an acute psychosis due to intoxication from undulant fever The persistence of the psychosis after the physical signs of intoxication had disappeared is, of course, not unusual in toxic psychosis

According to Rogei ² the appearance of psychic disturbances in undulant fever has an unfavorable prognostic significance, 10 of the cases which he collected from the literature died

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PROTAMINE INSULIN AS A CONTRIBUTING FACTOR IN THE DEATH OF A DIABETIC PATIENT WITH CEREBRAL ARTERIOSCLEROSIS

By JANVIER W LINDSAY, M D, F A C P, E CLARENCE RICE, M D, F A C P,
MAURICE A SELINGER, M D, and K HAMMOND MISH, M D,
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PROTAMINE insulin was first used in the United States during 1935 by Root,¹ Joslin² and then associates and since then its use has been extended to diabetic patients in other parts of the country under the direction of physicians with considerable experience in the treatment of diabetes mellitus The number under treatment at present in the United States is probably about 3,000 persons

By means of its use it has been possible to convert the severe diabetes of a number of patients not easily controlled by the simpler or regular insulin to a relatively mild form due to the prolonged action of the new insulin which often eliminates the sudden and wide excursions of the blood sugar, replacing these with a flatter type of curve Various other advantages accruing to the patient

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From the Garfield Memorial Hospital, Washington, D C

from its uses, such as the reduction in the daily number of injections, the elimination of insulin reactions or the lessening of their severity when hypoglycemia was present, have been observed as compared with the results obtained and effects noted, from the previous use of regular or simpler insulin

Joslin² cautioned against the possible dangers from hypoglycemia, especially if two doses of protamine insulin were used. We have used protamine insulin † since January 1936, in the treatment of over 30 patients and at all times have kept in mind its possible dangers. It is because of a fatality occurring during the treatment of one of our diabetic patients with protamine insulin and because of the possibility that the initial coma, which ended in death, was due to prolonged and extreme hypoglycemia resulting from the long action and cumulative effect of the new insulin, that we present the following case report

CASE REPORT

The patient, an unmarried white female, a clerk, developed diabetes mellitus at the age of 44, during the latter part of 1931. Since the onset she had lost 71 pounds (32.3 kg) when first seen in the diabetic clinic on August 26, 1933, had been treated by dietary restriction alone. Subsequent to this a sister developed diabetes following the removal of a goiter and died in coma, and a brother was found by other physicians to have a glycosuria.

At the time of her initial treatment by us she gave no evidence of arteriosclerosis and the only findings of note were evident anemia and a fibroid uterus. Blood pressure averaged 120 systolic and 80 diastolic. The Wassermann and Kahn tests were negative. Following a three week period of unsuccessful dietary treatment she was given standard insulin in increasing doses. On a diet of carbohydrate 90 gm, protein 54 gm and fat 78 gm, she required 4 doses of insulin averaging 18-12-15-7 units daily. Occasional insulin reactions were experienced. Following a period of hospitalization her diabetes was better controlled on carbohydrate 80 gm, protein 43 gm, and 72 gm of fat with insulin in doses of 16-8-12-11 units per day. In May 1934, her basal metabolic rate was minus 5 per cent. Her electrocardiogram showed complexes of low amplitude, with T_{1-2} nearly isoelectric. Her weight had increased from 134 pounds (60.9 kg) to 172 (78.2 kg). In August 1934, because of the hours of her employment her insulin dosage was 22-14-0-12. From this time until April 1936 her diabetes was never satisfactorily controlled, post-prandial blood sugars varying between 244 and 400 mg. In October 1934, she became comatose at night during an insulin reaction, the incident being preceded by a severe diarrhea.

On April 1, 1936, on a diet of carbohydrate 110 gm, protein 50 gm, and fat 61 gm, she excreted 64 gm of dextrose during the 24 hours. Protamine insulin was started on April 4, 1936, with immediate improvement in the control of the patient's diabetes. Subsequent treatment with the new insulin changed the diabetes from severe to relatively mild on the basis of ease of control. A synopsis of treatment is given in table 1.

Throughout the treatment of the patient considerable difficulty was experienced by the staff of the diabetic clinic in maintaining proper contact. Due to her reduced financial status she rarely felt able to take sick leave to attend the clinic oftener than every two weeks. Although she was able to come to the hospital laboratory for blood examinations on Sundays and after work, those attending her were rarely able to meet her at these times. Instructions were often given by letter. During the latter part of August 1936, when notes from the patient stated that she was having insulin

† Supplied by Eli Lilly & Co., Inc., Indianapolis, Ind.

TABLE I

Date	Weight Lbs	Blood Sugar Mg per 100 cc	Time	Insulin		Urine					Remarks
				Regular Units	Protamine Units	24 hr Dex- trose Gm	7 a m	Noon	6 p m	10 p m	
3/31/36	165	400	Fasting	22 0 13 5 = 40			3 +	—	3 +	3 +	Insulin prota- mine started
4/12/36	169			22 0 13 5 = 40		61 0	3 +	—	3 +	3 +	
4/14/36	169			20 0 15 0 = 35	8 0 6 0 = 14		3 +	—	3 +	3 +	
4/17/36	169	222	3 00 p m	15 0 13 0 = 28	8 0 6 0 = 11		0	—	1 +	3 +	
4/18/36		250	Fasting	15 0 13 0 = 28	8 0 6 0 = 14		0	—	3 +	1 +	
5/12/36	172	166	3 00 p m	12 0 14 0 = 26	12 0 6 0 = 18	26 4	0	—	3 +	0	
5/17/36		235	Fasting	10 0 13 0 = 23	11 0 6 0 = 20		0	—	2 +	1	Some evidence of hypoglycemia before lunch
5/31/36	174	100	11 00 a m	6 0 11 0 = 20	18 0 8 0 = 26		0	—	3 +	1 +	
6/ 7/36	174			6 0 14 0 = 20	18 0 8 0 = 26	16 4	0	—	3 +	1 +	
6/ 9/36	174	250	3 00 p m	6 0 14 0 = 20	18 0 8 0 = 26		0	—	2 +	1 +	
6/16/36	174			6 0 10 0 = 16	22 0 12 0 = 31		0	—	3 +	1 +	
6/23/36	176	300	3 00 p m	0 0 12 0 = 12	30 0 10 0 = 40		0	—	3 +	0	
7/12/36	173			0 0 10 0 = 10	32 0 8 0 = 40	15 6	0	—	2 +	0	
7/14/36	173			0 0 10 0 = 10	32 0 8 0 = 40		0	—	0	0	Reaction at 10 a m 4 p m, and midnight
7/19/36	171	396	Fasting	0 0 4 0 = 4	36 0 8 0 = 42		0	—	2 +	1 +	Insulin prota- mine with cal- cium started
7/21/36	171	222	2 00 p m	0 0 0 0 = 0	36 0 8 0 = 42		0	—	1 +	3 +	
7/22/36	170	414	Fasting	0 0 0 0 = 0	40 0 0 0 = 40		0	—	2 +	2 +	
7/28/36	170	206	2 30 p m	0 0 5 0 = 5	40 0 0 0 = 40		0	—	3 +	2 +	Unconscious at 11 30 p m
7/29/36	170	200	5 30 p m	0 0 0 0 = 0	40 0 0 0 = 40		0	—	1 +	0	
8/ 3/36	170	208	Fasting	0 0 6 0 = 6	40 0 0 0 = 40		0	—	3 +	0	
8/ 4/36	170	200	Fasting	0 0 0 0 = 0	38 0 12 0 = 50		0	—	2 +	0	
8/19/36	170			0 0 0 0 = 0	38 0 12 0 = 50		0	—	1 +	0	Reaction at 6 a m Dazed en- tire day Un- able to work Vertigo at 5 30 p m Sweating at midnight Vertigo
8/20/36	170			0 0 0 0 = 0	36 0 10 0 = 46		0	—	0	0	
8/21/36	170			0 0 0 0 = 0	36 0 10 0 = 46		0	—	0	0	
8/22/36	170			0 0 0 0 = 0	30 0 10 0 = 40		0	—	0	0	
8/25/36	170	200	5 00 p m	0 0 0 0 = 0	30 0 10 0 = 40		0	—	0	0	
8/30/36	170	250	11 00 a m	0 0 0 0 = 0	30 0 10 0 = 40		0	—	0	0	Insulin reaction at 2 00 a m and chill at 6 00 a m
8/31/36 to 9/ 3/36			No record kept by patient Diet C 110 P 50 F 61								

reactions, a number of attempts to communicate by telephone were made without success

On the afternoon of September 3, 1936, a neighbor noticed that the bottled milk delivered to the patient's home that morning had not been removed from the front porch. Upon investigation the patient was found partially dressed and lying unconscious across her bed. One of us (K H M) was called to see the patient and at 5 30 p m found her comatose, with rapid pulse and flaccid extremities. There was no evidence of food having been eaten at any time during the day. Whether or not the morning dose of 30 units of protamine insulin had been taken following the injection of 10 units the night before is not known. One resident in the house reported talking to the patient about 10 00 p m on the previous day, at which time she seemed to be quite normal. Other residents of the home stated that they heard her moving about her quarters between 6 and 7 a m, but no one saw her on September 3, until discovered by the neighbor. The circumstances and findings were believed to be sufficient to warrant a tentative diagnosis of coma due to hypoglycemia. Ten cubic centimeters of 50 per cent dextrose solution were given intravenously without

demonstrable effect at 5 45 p m She was removed to the hospital and admitted there at 6 45 p m

The following additional history was obtained from relatives after admission to the hospital For three weeks prior to September 3, the patient had lived alone in her apartment, her mother who lived with her being out of the city on a visit Her mother stated that several days before she vacated the apartment the patient came home from office in a daze having no recollection of how she reached there after leaving the street car which brought her from work

Examination revealed the findings as noted above, the skin was cool, the tongue was blue, pulse was rapid and thready, breathing labored Rectal temperature was 100° F Blood sugar, 75 minutes after the intravenous injection, was 307 mg Immediately after this 500 c c of 20 per cent dextrose in normal salt solution were given intravenously At 8 30 p m the blood sugar was 500 She seemed to react favorably for a short time during the intravenous injection but returned to the comatose state The circulation improved, the pulse slowing to 100, blood pressure rising to 140 systolic and 85 diastolic Pupils were equal in size and moderately contracted, reacting to light A lateral nystagmus was observed The lower jaw moved with a chewing movement There appeared to be some paresis of the muscles of the right side of the face and saliva drooled from the mouth The extremities were flaccid and knee jerks absent The Babinski and Kernig tests and ankle clonus were absent There was some slight reaction to deep pressure over the bladder

The bladder was catheterized and 60 c c of urine obtained Except for the presence of a large amount of sugar it was normal chemically and microscopically Spinal fluid withdrawn at 9 00 p m was normal, except for the total amount of sugar 165 mg Pressure was normal The electrocardiogram showed no change from one done two years previously At 9 30 p m a generalized convulsion lasting one minute followed by a few minutes of spasticity, was observed A second convulsion occurred at 10 00 p m At 11 00 p m, blood chemical tests gave the following results non-protein nitrogen 34 mg per cent, sugar 380 mg per cent, carbon dioxide combining power 51 volumes per cent

At 1 00 a m, September 4, a convulsion lasting one minute occurred Following this, 200 c c of 20 per cent dextrose in normal salt solution were given The results of further treatment and laboratory examinations are summarized in table 2

Neurological examination at 3 15 p m, September 4, by Dr Philip Litvin showed "the patient to be in coma There was a slight lateral nystagmus, more marked to the right The pupils alternately contracted and dilated, remaining in a somewhat contracted condition There appeared to be some weakness of the right side of the face, but this was not definite A flaccid paralysis of the upper and lower extremities was observed with a slightly positive Babinski test on the right, that on the left being markedly so Impression Cerebral infarct, probably as a result of old diabetes "

The patient's condition remained about the same on the fifth and sixth Neurological examination on the latter date by Dr D D V Stuart, Jr, gave the following result "Slightly contracted pupils, regular and symmetrical, which respond to light Cervical sympathetic response intact Slow lateral oscillatory movement of the eye balls (not a nystagmus) Corneal reflexes absent The ocular fundi were not well seen, but there appeared to be no abnormalities of the discs or the vessels The deep reflexes were absent The right pectoral reflex was present and a slight movement of both feet was noted on stroking the plantar surfaces A slight odor of acetone was noted on the breath Impression No clinical evidence of cerebrovascular lesion The condition was believed to be primarily diabetic and an increased amount of insulin suggested if the spinal fluid sugar content was above 75 mg/100 "

Spinal fluid removed September 8 showed 6 mm of mercury pressure with 380 erythrocytes and 2 leukocytes per cubic millimeter That on the tenth was under

reduced pressure with innumerable red blood cells and 10 white blood cells per cubic millimeter. The presence of free blood was believed to be due to trauma and of no clinical significance, the supernatant centrifuged fluid being colorless. The Wassermann reaction was negative.

The patient remained comatose until death occurred on September 11, at 11 30 p m, a total of eight days. During the illness the rectal temperature gradually rose from 100° F to 105.8°, pulse varied between 100 and 140, respirations between 20 and 30, except during the last two days, when they averaged 40 per minute. Blood pressure averaged 130 systolic, 86 diastolic during the greater part of the illness. Sweating was most profuse at all times. Beginning September 6, nourishment was

TABLE II

Date	Nourishment	Blood Chemistry						Urine			In sulin Units	Remarks
		Sugar	N P N	Chlo rides	Ca	In org Phos	CO Comb Power	Sugar	Acetone	Di acetic Acid		
9/3/36 5 45 p m 7 00 p m 7 15 p m	10 c c 50% dextrose (V) 500 c c 20% dextrose (V) in normal NaCl sol	307 500										B P 140/85 Convulsion Convulsion
8 30 p m 9 30 p m 10 00 p m 10 30 p m 11 15 p m		380	34				51	4+	0	0		
9/4/36 2 00 a m	200 c c 20% dextrose (V) in Hartman's solution	285		454	8.0	3.3		4+	0	0		Convulsion B P 94/60 1 gm calcium gluconate intrav
3 00 p m		324					30	4+	0	0		1 gm calcium gluconate intrav
8 00 p m	250 c c 5% dextrose (V) in Hartman's sol											B P 112/76 RBC 4 670 000 WBC 21 200 Hb 14.8 gm /100 c c P 96%, L 4%
9 30 p m 12 00 p m								3+	+	+		
9/5/36 12 30 a m 4 00 a m								3+	+	0	15 15	WBC 16 500, P 96% L 4% B P 142/94
6 00 a m 8 00 a m 11 00 a m	1 000 c c 5% dextrose (V) in normal NaCl sol	222					36	3+	+	0	15	
5 00 p m 8 00 p m 9 00 p m	1 000 c c 5% dextrose (V) in normal NaCl sol							3+	+	0	2, 130 1, 30 15	B P 126/86
9/6/36 1 45 a m 5 15 a m 8 30 a m 3 00 p m 7 00 p m 11 30 p m	C 106 P 24 F 10 (by tube feedings)							3+	+	0	15 15 75	B P 152/90
								3+	+	0	15	
								0	+	0	15	
								2+	0	0	15	
								3+	0	0	15	
								3+	0	0	15	
9/7/36 3 00 a m 7 00 a m 11 15 a m 12 00 a m	C 234 P 36 F 15 (by tube feedings)	333						3+	+	0	15 15	B P 140/00 1 000 c c Normal NaCl sol subcutaneously
								3+	+	0	15	
								1+	0	0	105	

TABLE II—Continued

Date	Nourishment	Blood Chemistry						Urine			In- sulin Units	Remarks
		Sjg ar	NPN	Chlo rides	Ca	In- org Phos	CO Comb Power	Sug ar	Acc tone	Di acetic Acid		
3 00 p m 7 00 p m 11 00 p m	C 204 P 54 F 54 (by tube feedings)							3+	+	0	20	101 B P 120/80 1 000 c c Normal NaCl sol subcutaneously
								3+	+	0	20	
								3+	+	0	20	
								2+	0	0	12	
								2+	0	0	12	
3 00 p m 7 00 p m 10 20 p m 11 00 p m	C 204 P 54 F 54 (by tube feedings)	250						3+	0	0	20	112 B P 120/88 1 000 c c Normal NaCl sol subcutaneously
		204						4+	0	0	24	
								1+	0	0	5	
								3+	0	0	20	
								3+	+	0	20	
3 00 a m 7 00 a m 11 00 a m	C 204 P 54 F 54 (by tube feedings)							3+	0	0	20	195 B P 128/86 B P 110/80 1 500 c c normal NaCl sol subcutaneously 300 c c tap water by bowel R B C 5 330 000 000 Hgb 15 gm /100 c c W B C 20 000 P 74% L 16% Endo 5% Turk 2% Baso 1% Eosin 2%
								3+	0	0	20	
								3+	0	0	20	
								1+	0	0	5	
								1+	0	0	5	
3 00 p m 7 30 p m 12 00 p m	C 204 P 54 F 54 (by tube feedings)							3+	0	0	20	71 300 c c tap water by bowel B P 100/86 1 500 c c normal NaCl sol subcutaneously 300 c c tap water by bowel B P 89/65 1 000 c c 5% dextrose sol intravenously Death
								3+	0	0	20	
								2+	0	0	12	
								3+	+	0	20	
								3+	0	0	20	
9/10/36	C 204 P 54 F 54 (by tube feedings)	333	56	528			60	3+	+	0	20	71 300 c c tap water by bowel B P 100/86 1 500 c c normal NaCl sol subcutaneously 300 c c tap water by bowel B P 89/65 1 000 c c 5% dextrose sol intravenously Death
3 00 a m 7 00 a m 11 00 a m								3+	0	0	20	
								3+	0	0	20	
								3+	0	0	20	
								1+	0	0	5	
2 30 p m	C 204 P 54 F 54 (by tube feedings)							3+	0	0	20	71 300 c c tap water by bowel B P 100/86 1 500 c c normal NaCl sol subcutaneously 300 c c tap water by bowel B P 89/65 1 000 c c 5% dextrose sol intravenously Death
								3+	0	0	20	
								3+	0	0	20	
								3+	0	0	20	
								1+	0	0	6	
7 00 p m	C 266 P 39 F 39 (by tube feedings and intrav)							3+	0	0	20	71 300 c c tap water by bowel B P 100/86 1 500 c c normal NaCl sol subcutaneously 300 c c tap water by bowel B P 89/65 1 000 c c 5% dextrose sol intravenously Death
								3+	0	0	20	
								3+	0	0	20	
								3+	0	0	20	
								1+	0	0	6	
11 00 p m	C 266 P 39 F 39 (by tube feedings and intrav)							3+	0	0	20	71 300 c c tap water by bowel B P 100/86 1 500 c c normal NaCl sol subcutaneously 300 c c tap water by bowel B P 89/65 1 000 c c 5% dextrose sol intravenously Death
								3+	0	0	20	
								3+	0	0	20	
								3+	0	0	20	
								1+	0	0	6	
9/11/36	C 266 P 39 F 39 (by tube feedings and intrav)							3+	+	0	20	71 300 c c tap water by bowel B P 100/86 1 500 c c normal NaCl sol subcutaneously 300 c c tap water by bowel B P 89/65 1 000 c c 5% dextrose sol intravenously Death
3 00 a m 7 00 a m 11 00 a m								1+	0	0	5	
								3+	0	0	20	
								3+	0	0	20	
								3+	0	0	20	
3 00 p m 7 00 p m 8 30 p m 11 00 p m 11 30 p m	C 266 P 39 F 39 (by tube feedings and intrav)							1+	0	0	6	71 300 c c tap water by bowel B P 100/86 1 500 c c normal NaCl sol subcutaneously 300 c c tap water by bowel B P 89/65 1 000 c c 5% dextrose sol intravenously Death
								1+	0	0	6	
								1+	0	0	6	
								1+	0	0	6	
								1+	0	0	6	

given by tube feedings with one liter of normal salt solution subcutaneously daily, a daily total fluid of 3,100 c c being given

Necropsy was performed 11 hours after death. The findings are summarized as follows. The lungs showed passive congestion and superficial atelectasis. The heart was of normal size, the musculature being soft, and on microscopic examination giving evidence of myocardial degenerative change. The mitral valve was thickened and the coronary arteries showed moderate atheromatous changes as did the aorta. The liver was the site of fatty degeneration and chronic passive congestion. The pancreas weighed 50 gm and was unusually soft and hyperemic. On microscopic examination there was found an increase in interstitial connective tissue, the acinar tissue being hyperplastic. Granular degeneration was marked and islet tissue was but rarely recognized. The kidneys showed parenchymatous degeneration, moderate

interstitial fibrosis, but little vascular change. The uterus was twice the normal size, due to a nodular fibroid tumor in the fundus, it being retroverted and bound down firmly to the sigmoid. The left tube and ovary were intimately enmeshed in these adhesions. *B. cloacae* was cultured from the heart's blood.

The most striking changes were noted in the brain, which externally exhibited nothing unusual. The superior surface of the pituitary body was flattened suggesting the probability of increased intracranial pressure. On section the left cerebral hemisphere showed occasional scattered punctate hemorrhagic areas within the cortex and very rarely in the deeper structures. Connected with one of the fissures in the occipito-parietal region was found a cystic space approximately 1.5 cm in diameter, the outer portion lined by typical gray matter, the deeper portions eroded, the wall being covered by a fine fibrinous material. This space is believed to be the result of pressure from fluid accumulating within the fissure, possibly blood which was later absorbed. Section of the right hemisphere revealed more numerous punctate hemorrhages and a smaller cystic space than that described above, lying near the medial surface of the occipital lobe. No gross evidence of thrombus within or hemorrhagic infiltration outside the vessels of the internal capsule was noted.

Microscopic examination. "The right occipito-parietal lobe and the right internal capsule are markedly edematous with perivascular accumulations of fluid. The vessels appear to be sclerotic and calcification of their walls is seen. The appearance suggests a moderate increase in glial tissue. The left internal capsule is very edematous and small foci of degeneration are noted. Small extravasations of blood and some pigment is found about the vessels. Rather similar findings are observed in the left pons. Sections through the choroid plexus of the left lateral ventricle show the ependyma to be normal. The plexus is congested and edematous with some tendency to epithelial desquamation. Many arterioles are completely occluded by calcific thrombi (?), while others show no change. The left choroid plexus in the third ventricle shows similar changes there also being calcium deposits bearing no definite relation to the blood vessels. These appear to be true psammoma. The cyst wall is represented by fragmented bodies of degenerated parenchyma presenting no evident surrounding inflammatory reaction. The cavity is lined by debris which contains many large beaded bacillary forms. In many of the adjacent blood vessels these organisms can be seen, some appearing to form thrombi. The pituitary body is markedly edematous, the basophilic elements predominating."

COMMENT

The history obtained from the patient, relatives and friends indicates that she probably experienced the effects of a relatively low blood sugar on a number of occasions during the late afternoon and evening or early morning over a period of two months preceding her death. Although the lowest blood sugar obtained at any time was 100 mg/100 cc, it seems likely that lower levels were reached during some of the above mentioned periods, however, no examinations of the blood were made at any time between 5.30 p.m. and 8.00 a.m. Persons living in the same building with the patient stated that during the early part of her treatment with protamine insulin she frequently ate more than her diet called for, but that later on she closely adhered to it.

In view of the marked cerebral arteriosclerosis and the maintenance of the blood pressure at a level slightly below normal, it would appear that the patient was more than ordinarily susceptible to the effects of a relatively low blood sugar. We believe that the result of lowering the blood sugar level in this patient to a point considerably below normal would have an effect analogous to

that obtained in a diabetic individual with marked coronary artery sclerosis. Many of the physical findings observed after unconsciousness was noted, are frequently seen in coma due to insulin hypoglycemia, viz., tonic and clonic muscle spasm, lateral movements of the eyeballs and positive Babinski.

Attention is called to the similarity of this case report and Bowen and Beck's³ case 2, with necropsy findings in the brain by Teiplan⁴. White⁵ also mentions the case of a child, who died as a result of hypoglycemia and on whom a complete necropsy was performed, with findings quite similar to ours. The presence of cerebral arteriosclerosis represents the most important point of difference between the pathological changes in the brain of our patient and those mentioned above. Due to the narrowing of the vessels, a reduced amount of dextrose was supplied to the brain unless the blood sugar was maintained above the usual normal. We feel that this abnormality may have caused her to react to the effects of hypoglycemia when the amount of sugar in her blood was lowered to a level which would not have brought on marked symptoms of hypoglycemia in a patient not similarly affected.

At the time of admission to the hospital in a comatose state, the blood sugar was 307 mg, however, the next morning after a total of 145 gm of dextrose had been given intravenously, no insulin having been administered for 24 hours the amount in the blood was 285 mg. Although one neurological consultant felt that the patient's unconscious state was due to acidosis and insufficient insulin, we do not believe that ketosis was a significant factor at any time, inasmuch as the carbon dioxide combining power on hospitalization was 51 volumes per cent and neither acetone nor diacetic acid was present in the urine. The lowest carbon dioxide combining power recorded was 30, on the second day of coma. Diacetic acid was found in the urine once during the course of the illness, over 40 specimens being examined.

Although there is insufficient laboratory evidence to prove conclusively that the patient's coma was caused by insulin hypoglycemia, we feel that the available data strongly support the view that such a condition was an important factor in its production. The possible dangers incident to the use of any insulin preparation with prolonged action and cumulative effect are emphasized. Until the actions of such preparations are more definitely known we feel that their use should be restricted to those who can be kept under rather constant supervision and control.

SUMMARY

- 1 In the case reported, the difficulties in the control of the patient's diabetes were greatly reduced following the use of protamine insulin, however, reactions attributed to insulin hypoglycemia were accentuated.

- 2 Unconsciousness, believed to be due to prolonged and possibly severe hypoglycemia resulting from the cumulative effect of protamine insulin was observed.

- 3 Death followed eight days coma. Necropsy revealed cerebral arteriosclerosis and cerebral edema with some degenerative changes in the brain.

- 4 The possible dangers to the patient from the prolonged and cumulative effect of the more complex insulin preparations are noted.

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- 3 BOWEN, B D, and BECK, G Insulin hypoglycemia, ANN INT MED, 1933, vi, 1412
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EDITORIAL

DISCREPANCY BETWEEN EXPERIMENTAL AND CLINICAL KNOWLEDGE OF THE ANTERIOR PITUITARY BODY

VAN DYCKE recently has written a book, "The Physiology and Pharmacology of the Pituitary Body," during the course of which he reviewed more than 5,000 articles. The bibliography fills 200 pages and yet contains but few references to clinical articles. What is most amazing is that practically all of these articles were written within the past 15 years. So many articles are being published in this field that it is virtually impossible for any practicing physician to keep informed regarding this rapidly accumulating knowledge. He is forced to rely on reviews, most of which are very good but all of which reflect the reviewer's sympathies and prejudices. Or he may rely on the publications of commercial houses some of which are good but many of which are cursory and misleading.

In general there are two groups of such articles. The first group comprises those published by workers in the fundamental fields of biology, chemistry, physiology, pathology, anatomy, and so on. Most of these represent excellent work, including detailed studies under carefully controlled conditions. However, an unprejudiced observer is impressed with the discrepancies existing even in this exact field. As an example one may mention the single factor of species difference. Results obtained with the use of one laboratory animal may be quite different when repeated in another laboratory with a different species. Differing methods of preparing the injected material, differing diets and environmental conditions for the animals, the use of animals of different sex or age—these and many other factors make the comparison of results very difficult. The result is that we do not know, for example, how many hormones of the anterior lobe of the pituitary can be regarded as accepted. Is there one gonadotropic hormone, or are there five? The one hormone which always has been above suspicion is the growth hormone, yet recently a voice has been raised to question its specificity.

The second group of articles in this field is that dealing with the clinical application of this knowledge. These articles as a group are far inferior to the first group mentioned. Many of them never should have been written and represent work which never should have been done. Extracts of uncertain character are injected into patients suffering from uncertain conditions and the misinterpreted results are published by indiscriminating editors. The result is extremely confusing to the clinician, particularly if he is being asked to see many patients supposedly suffering from "pituitary disease."

There are two major difficulties in attempting to evaluate the clinical application of our knowledge in this field. The first already has been touched

on, namely, the unsettled condition of our knowledge of the fundamental principles involved. It seems unwise to utilize clinically a hormone which is not understood biologically. Thyroid extract and insulin are used with good results because of the completion of fundamental studies before their use in the treatment of human beings was attempted. On the other hand, the thyiotropic and carbohydrate influencing principles of the pituitary are most interesting but much work remains for the laboratory before these substances should invade the treatment room. Van Dyke records more than 100 "hormones" now on the market which are obtained from the pituitary gland, sex glands, placenta, blood, or urine of animals or man. At the present writing no hormone from the feces is being marketed. Many of these 100 "hormones" are totally unsuited for injection into man.

The second difficulty is that we know so little about the clinical conditions which may arise from a disturbance of the pituitary. We know of acromegaly, dwarfism, Cushing's syndrome, and a few other well defined conditions. The difficulty is that these comprise such a small portion of the cases in which treatment is with pituitary hormones. The literature contains many references to the treatment of "hypopituitarism" and "hyperpituitarism." Such terms are so indefinite as to be meaningless.

Clinicians react to this situation in various ways. Some are busy utilizing "hormones" indiscriminately and are reporting their confusing results. Others have developed an inferiority complex because, in spite of genuine effort, they cannot obtain the dramatic cures which others report. Others are carefully utilizing standardized substances in the treatment of specific conditions and are reporting their negative as well as their positive results. Blessed are they! Others are simply waiting and hoping.

What can be suggested as a way to the solution of this confusion existing between experimental studies and clinical application? The first step might be for all responsible physicians to subscribe to the concluding paragraph in a recent editorial in the *Journal of the American Medical Association*. "These remarks are not intended to reflect upon the importance of the chemical and biological studies of accredited laboratories, the author is filled with admiration for such efforts. Neither do these remarks apply to the carefully controlled clinical application of accepted knowledge by competent observers, this is necessary. Rather are these remarks intended (1) to emphasize the fact recognized by many interested observers that there is a great discrepancy between our laboratory knowledge of the hormones and their clinical application, (2) to suggest that for the present only those clinicians with facilities for critical study be encouraged to inject extracts into patients and that these men be urged to publish their negative as well as their positive results, and (3) to suggest that the large group of physicians not represented in either group mentioned above cease their unstudied injection of unknown substances into unsuspecting patients."

E H R

REVIEWS

The Art of Treatment By WILLIAM R. HOUSTON, A.M., M.D., F.A.C.P. 744 pages, 16.5 × 24 cm. The Macmillan Co. New York. 1936. Price, \$5.00.

This work is described in the author's preface as a collection of the subject matter presented in a series of conferences with senior medical students and young doctors. The conference style is carried throughout and is always conducive to interest, although, at times, it does not lend itself very well to the subject.

A practical method is introduced for considering therapy in general. Diseases are grouped according to their chief method of treatment: by nursing care, specific psychotherapy or guidance, limitation of life, physiological consideration and experimental treatment. The common cold, typhoid fever and most of the acute specific infectious diseases are included among those diseases treated chiefly by nursing care; lobar pneumonia, in spite of its frequent treatment by specific sera, is also included in this group. It is easy to understand that this method of presentation has many practical advantages, as repetition is largely eliminated and therapeutic methods described in detail for one member of the group may apply with little or no modification to others.

The reviewer does not, however, agree with the author's decision in placing certain pathological conditions in the chosen groups of diseases. Thus, there seems to be no definite reason for including obesity, bronchiectasis and lung abscess among those treated by "limited living"; certainly the latter might better be grouped among those diseases treated by nursing care.

The author has evidently drawn on an extensive personal experience and his personality is reflected in his writing. There can be no doubt that he has done a valuable piece of work, especially in his discussion of therapeutic planning. The long introductory section is almost classical in its style, interest, and value.

A criticism that might be offered is that in certain cases discussion is too lengthy and actual advice too brief. For example, in outlining the treatment of exophthalmic goiter no very definite therapeutic plan is presented, the usual time required for iodine remission is not stated, and treatment of thyroid storm and cardiac complications is not mentioned. In the section on diabetes, advice is somewhat indefinite and treatment of complicating infection is hardly mentioned. Diabetic coma is not very well discussed.

The section on psychotherapy contains many very helpful suggestions for the management of the patient, but here, as elsewhere, the author tends to digress from the subject frequently, so that information may be somewhat obscured. The absence of an adequate chapter on physical therapeutic methods is disappointing.

The writing of a textbook on therapy is one of the most difficult tasks an author can undertake, but Dr. Houston's contribution should be a valuable addition to our current texts.

T. N. C.

Diseases of the Newborn By ABRAHAM TOW, M.D. 477 pages, 15.5 × 23 cm. Oxford University Press, New York, N.Y. 1937. Price, \$6.50.

In the compilation of this work Dr. Tow has been extremely thorough. Practically all of the conditions affecting the newly born have been covered. Even such rarities as the Klippel-Feil syndrome and osteopetrosis receive attention. At times the discussion is extended beyond the neo-natal period, but only in the interests of clarification or completeness. Sufficient stress is laid upon the clinical side of the

book to make it attractive to the practitioner. The literature has been exhaustively investigated and where differences of opinion exist the conflicting views are presented in an unbiased fashion. The author states in the preface "On basis of years of experience on the newborn service at the New York Polyclinic Hospital certain opinions have been formulated and there has been no hesitancy in expressing these opinions when it was felt that they might clarify a controversial subject." Case reports are frequently used to illustrate diagnosis, prognosis or treatment of various diseases or conditions, a method felt by the reviewer to be quite valuable.

An excellent bibliography follows each chapter. The references are well chosen and contain the most modern views on the various subjects.

Adequate use has been made of illustrations, most of which deal with congenital defects, birth injuries, and the apparatus for special pediatric procedures. A number of these pictures are rather blurred as to detail, a factor which makes their value questionable.

The print is of a close small type and the pages are highly glossed, a combination that for prolonged use is rather tiring.

The defects of this volume are more than compensated by its thoroughness and by the excellent presentation. It compares very favorably with other books dealing with this subject and should be of value to both the practitioner and pediatrician.

J E B

Practical Examination of Personality and Behavior Disorders. By K. E. APPEL and E. A. STRICKER. 219 pages, 15.5 × 22 cm. The Macmillan Company, New York. 1936. Price, \$2.00.

There are many things in this book which serve to make it both an interesting and useful volume. Although the authors have presented the book ostensibly for medical students and neophytes in psychiatry, they have included material which may have a wider appeal. The volume is divided into two parts, the first of which is devoted to the study of adult patients and the second to children. The presentation is given largely in a very accessible outline form. It is noteworthy for its simple style and absence of flowery verbiage.

The chapter on "The Art and Practice of the Psychiatric Examination" is especially practical and timely. Specific directions as to how to elicit material of psychiatric interest are given by the authors, together with some warnings and safeguards to be followed by the person conducting the examination. The general impression created is that which is so well known to the trained psychiatrist, namely, that the physician does not tell the patient everything that he knows about him.

Most of the remainder of the section on adults applies principally to the study of psychotic patients. More attention might have been paid to the neurotic group. The first chapter described in the previous paragraph could have been incorporated nicely with the chapter on "Suggestions for Making the Mental Examination."

The greatest value of the work, in the opinion of the reviewer, lies in the portion devoted to the examination of children. The technique of obtaining information from the child by entering his phantasy life is especially interesting and practical. There is considerable material, too, that serves a useful purpose in acquainting medical men with what is considered the most modern advice concerning the emotional needs of childhood. In this respect the book contains more material of a prophylactic or therapeutic nature than purely diagnostic.

In all it may be said that the book would be a valuable addition to the library of every practitioner of medicine.

J C S

The Diagnosis and Treatment of Diseases of the Heart By HENRY A. CHRISTIAN, M.D., Sc.D., LL.D., Hersey Professor of the Theory and Practice of Physic, Harvard University. 373 pages, 15.5 × 24 cm. Oxford University Press, New York. 1935. Price, \$6.00.

Dr. Christian writes interestingly and instructively of his experiences in regard to heart disease and its treatment. He emphasizes that the practitioner should as a rule be able to arrive at a cardiac diagnosis without the aids of costly special examinations and that these latter methods should never replace clinical knowledge based on experience. The reviewer has noted that many men of ripe clinical experience arrive at such conclusions, nevertheless he feels that sufficient knowledge is gained at times to make such studies routine in cases of heart disease when practicable. If they serve no other purpose they convince the patient, in these days of public knowledge, that his case has been studied thoroughly. The indications for electrocardiography are discussed in a brief chapter but no detailed description of this subject is offered. There is no chapter on roentgenographic examination of the heart. In the introduction the author states that this book is not written for students nor as a reference work, hence no attempt has been made to make the bibliography complete and it is assumed that the reader has some previous knowledge of the etiology, pathology, etc. of heart diseases. Chapters are included on such recent investigations as total ablation of the thyroid in the treatment of heart disease, and the recent advances in the pharmacology of digitalis. In the latter the author finds confirmation of his opinion in regard to the value of tonic doses of digitalis in the treatment of heart disease. The introduction is an essay of itself which may be read with pleasure by everyone.

W. S. L., JR.

The Diagnosis and Treatment of Chronic Diseases of the Respiratory Tract By ELMER H. FUNK, M.D., and BURGESS GORDON, M.D. Reprinted from Oxford Monographs on Diagnosis and Treatment. 618 pages, 24.5 × 16.5 cm, illustrated. Oxford University Press, New York. 1936. Price, \$8.00.

This volume undertakes to cover the field of chronic pulmonary diseases. The authors have divided it into four main parts. Part one is devoted to a discussion of the general methods of diagnosis, the special diagnostic procedures, such as roentgen-ray bronchography, etc., and the various general and specific therapeutic procedures. Parts two, three and four take up in order diseases of the trachea, bronchi, lungs, pleura, pulmonary tuberculosis, intrathoracic new growths and diseases of the diaphragm.

The manner in which the authors treat the various subjects is briefly as follows: general discussion, etiology, pathology, clinical manifestations, physical signs, diagnosis, and treatment. Along with this are included numerous helpful roentgen-ray plates, a few case histories, and a number of valuable references.

To cover the entire field of the chronic pulmonary diseases in such a thorough and concise manner requires painstaking efforts. The authors have achieved this end admirably and present us with a volume which can be safely recommended as a clear, concise, and valuable text.

H. V. L.

COLLEGE NEWS NOTES

GIFTS TO THE COLLEGE LIBRARY

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members

Books

- Dr J N Hall (Fellow), Denver, Colo, "Tales of Pioneer Practice"
Dr Samuel A Loewenberg (Fellow), Philadelphia, Pa, "Clinical Endocrinology",
Dr Frederick R Taylor (Fellow), High Point N C, a bound pamphlet containing page reprints and new material added to the chapter on "Unusual Diseases and Symptom-Complexes not Discussed in Other Chapters," from the Oxford Loose-Leaf Medicine,
United Hospital Fund of New York, Volume II of the "Hospital Survey of New York"

Reprints

- Dr Miles J Breuer (Fellow), Lincoln, Nebr, 2 reprints—"The Ideal and the Real in Medical Practice" and "The Treatment of Chronic Infectious Arthritis",
Major J R Darnall (Fellow), M C, U S A, 2 reprints—"War Service with an Evacuation Hospital" and "Diabetic Coma",
Dr Jacob Gutman (Fellow) Brooklyn, N Y, 9 reprints—
"The Use of Modern Drugs in the Treatment of Disease"
"The Use of Modern Drugs in the Treatment of Disease, I"
"The Use of Modern Drugs in the Treatment of Disease, II"
"The Use of Modern Drugs in the Treatment of Disease, III,"
"The Use of Modern Drugs in the Treatment of Disease, IV,"
"The Use of Modern Drugs in the Treatment of Disease, V,"
"Endocrine Disorders of the Female Sex, Their Causes and Correction,"
"Acidosis and Alkalosis Their Significance and Treatment" and
"Pituitary Hormones and Their Functions",
Dr Donald S King (Fellow), Boston, Mass, 2 reprints—"Hemorrhagic Bronchiectasis and Its Surgical Cure" and "The Middle Lobe of the Right Lung Its Roentgen Appearance in Health and Disease"
Dr George R Minot (Fellow), Boston, Mass, 1 reprint—"Investigation and Teaching in the Field of the Social Component of Medicine",
Dr William H Ordway (Fellow) Mount McGregor, N Y, 1 reprint—"An Interpretation of the Nature of Hodgkin's Disease",
Dr Kenneth Phillips (Fellow), Miami, Fla, 1 reprint—"Studies on the Neutralization Test of Gastric Acidity in Relation to General Disease",
Major James Stevens Simmons (Fellow), M C, U S A, 1 reprint—"Observations on the Importance of *Anopheles Punctimacula* as a Malaria Vector in Panama, and Report of Experimental Infections in *A Neomaculipalpus*, *A Apicimacula*, and *A Eisei*",
Dr Clan L Stealy (Fellow), San Diego, Calif, 1 reprint—"The Pollen Content of the Air of San Diego, California",
Dr Hyman I Goldstein (Associate), Camden, N J, 1 reprint—"Some Historical Notes on Allergy"

At the 84th annual meeting of the North Carolina State Medical Society, Dr Wingate M Johnson (Fellow) of Winston-Salem was installed as President and Dr James B Sidbury (Fellow) of Wilmington was made President-Elect for the coming year

Dr Virgil E Simpson (Fellow), Clinical Professor of Medicine, University of Louisville School of Medicine, delivered the Oration in Medicine at the annual meeting of the Illinois State Medical Association on May 18, 1937

The third annual meeting of the Federation of American Sanatoria (a national association of chest physicians) was held at Atlantic City, N J, June 7 to 11, under the Presidency of Dr William Devitt (Fellow), Allenwood, Pa Dr Edward W Hayes (Fellow), Monrovia, Calif, was installed as the new President Dr Frank Walton Burge (Fellow), Philadelphia, Pa, was Chairman of the Committee on General Arrangements, Dr Clyde M Fish (Fellow), Pleasantville, N J, was Chairman of the Committee on Entertainment The Vice-Presidents of the Federation for the past year included Dr Charles H Cocke (Fellow), Asheville, N C, Dr Louis Mark (Fellow), Columbus, Ohio, Dr George Foster Herben (Fellow), Loomis, N Y, Dr Ralph C Matson (Fellow), Portland, Ore, and Dr Samuel H Watson (Fellow), Tucson, Ariz Dr Charles M Hendricks (Fellow) of El Paso, Texas, is Chairman and Editor-in-Chief of the Federation's journal

At the opening administrative session, addresses were made by Drs Burge Devitt and Hayes Dr J Arthur Myers (Fellow), Minneapolis, Minn, delivered the address at the luncheon meeting on June 7 Dr Marcus W Newcomb (Fellow), Browns Mills, N J, delivered an address on "The Early Diagnosis of Pulmonary Tuberculosis", Dr Frank Walton Burge (Fellow), Philadelphia, delivered an address on "Bronchography" Dr William Egbert Robertson (Fellow), Philadelphia, was a guest speaker at the Banquet at which Dr William C Voorsanger (Fellow) San Francisco, was the toastmaster

Dr Anita M Muhl (Fellow), San Diego, Calif, has recently completed her postgraduate work at Johns Hopkins University and is spending an indefinite period in Europe She will attend the Medical Women's International Association convention at Edinburgh, Scotland, July 12 to 18, and the Second International Congress on Mental Hygiene in Paris, France, the week following

Dr Thomas B Magath (Fellow) of the Mayo Clinic has been appointed Health Officer of the city of Rochester He succeeds Dr Charles H Mayo who has been Health Officer for twenty-five years

The Council on Diabetes of the Public Health Federation, of which Dr Cecil Striker (Fellow) is Chairman, had a "Diabetic Day" with clinics in the morning and a round table luncheon meeting and a meeting of the Academy of Medicine of Cincinnati Dr Russell M Wilder of the Mayo Clinic discussed the medical aspects of diabetes and Dr A W Allen of the Massachusetts General Hospital the surgical aspects

Dr Cecil Striker was guest speaker of the Ohio State Dietetics Association April 13, at Columbus, Ohio, where he spoke on "Newer Concepts in Diabetes"

The Kansas section of the American College of Physicians met at the Menninger Clinic, 3617 West Sixth Avenue, Topeka, Kansas, Thursday, May 20 Dr Thomas

T Holt of Wichita, Governor of the American College of Physicians for Kansas, presided. Members who attended were Dr William H Algie of Kansas City, Kansas, Dr Ralph Ball of Manhattan, Dr James A Butin of Chanute, Dr Arthur Revell of Pittsburg, Dr Harold Jones of Winfield, Dr Harold Palmer of Wichita, Dr George F Corrigan of Wichita, Dr Kenneth L Druet of Salina, Dr Paul M Krall, of Kansas City, Kansas, Dr Fred McEwen of Wichita, Dr Philip Morgan of Emporia, Dr G A Westfall of Halstead, and Dr W C Menninger of Topeka.

Papers given were "Demonstration of Neurological Cases" by Drs Norman Reider and Harry Roback, Topeka. "Psychological Conflicts Expressed in Physical Symptoms Case Studies" by Dr Robert P Knight, Topeka. "Gastrointestinal Neuroses" by Dr W C Menninger, Topeka. "The Clinical Application of Endocrine Therapy" by Dr Ralph Ball, Manhattan. "Undulant Fever" by Dr Wm H Algie, Kansas City, Kansas. "Reports of Some Unusual Cardiac Cases" by Dr Fred McEwen, Wichita. "Some Aspects of a Group of Patients Who Were Examined on the Suspicion of Heart Disease" by Dr Philip Morgan, Emporia. "Impotence and Frigidity" by Dr Karl A Menninger, Topeka.

In addition to the members, many guests attended the program. Out of town guests of the Section included Dr Frank Moorhead of Neodesha, Dr George Seitz of Salina, Dr R R Sheldon of Salina, Dr N P Sherwood of Lawrence, Dr Maurice Snyder of Salina, Dr Charles Underwood of Emporia, Drs Frank Koenig and John Russell of Osawatomie, Dr Earl Vermillion of Salina, Dr M W Husband of Manhattan, Dr Ralph I Canuteson of Lawrence, Dr Henry Benning of Waverly, and Dr Allen Olson of Wichita.

Topeka doctors who attended were Dr R B Stewart, Dr Luenus E Eckles, Dr Leslie Saylor, Dr F A Taggart, Dr J A Crabb, Dr C F Menninger, Dr Robert P Knight, Dr C W Tidd, Dr Norman Reider, Dr Karl A Menninger, Dr C C Carlson, Dr Bernard Kamm, Dr William C Menninger, Dr Martin Grotjahn, Dr H N Roback, Dr Byron L Shifflet, Dr Joseph Pessin, Dr Robert T Morse, and Dr Eugene Eisner.

The program began at ten in the morning and continued all day with a barbecue supper at Indian Hill, Dr Karl Menninger's country home, in the evening.

Dr William Paul Holbrook (Fellow), Tucson, has been elected Vice-President of the Arizona State Medical Association.

Dr Francis G Blake (Fellow and College Governor for Connecticut), Sterling Professor of Medicine, Yale University School of Medicine, was a guest speaker at the annual scientific assembly of the Medical Society of the District of Columbia on May 5 and 6, his subject being "Serum Therapy in Pneumonia." Other members of the College participating on the program were Dr Arthur C Christie (Fellow), Washington, "The Socialization of Medicine To What Extent Is It Desirable?", Dr Walter Freeman (Fellow), Washington, "The Surgical Treatment of Mental Disorders", and Dr Henry B Gwynn (Associate), Washington, "Artificial Fever Therapy of Gonorrheal Arthritis."

Dr Charles Franklin Craig (Fellow), Professor of Tropical Medicine, Tulane University of Louisiana School of Medicine, New Orleans, addressed the eighty-eighth annual session of the Medical Association of Georgia at Macon, May 11 to 14, on "Tropical Diseases of Interest to Southern Physicians."

The seventy-eighth annual session of the Kansas Medical Society was held at Topeka, May 3 to 6. The following Fellows of the College were guest speakers: Dr Elliott P Joslin, Boston, "The Diabetic as a Surgical and an Obstetrical Risk", Dr Archibald L Hoyne, Chicago, "Progress in the Treatment of Meningococcic Meningitis", Dr Russell L Haden, Cleveland, "Clinical Approach to the Rheumatic Problem".

Dr Philip W Brown (Fellow), Rochester Minn, presented a lecture on "The Management of Diarrheas" before the annual graduate assembly of the Harrisburg (Pa) Academy of Medicine, May 27.

Sir Frederick G Banting (Fellow), Toronto, Ont, was one of the speakers on the symposium on recent progress in science on the occasion of the dedication of the new building of the Mellon Institute for Industrial Research in Pittsburgh early in May.

Dr William S Middleton (Fellow) Madison, Wis, and Dr Logan Clendenning (Fellow), Kansas City, Mo, presented papers on "William Wood Gerhard" and "The Medical Winning of the West," respectively, before the thirteenth annual meeting of the American Association of the History of Medicine at Atlantic City, N J, May 3. The meeting commemorated William Wood Gerhard's differentiation of typhus from typhoid one hundred years ago.

Dr Rufus I Cole (Fellow), New York City, addressed the annual Conference of State and Provincial Health Authorities of North America at Washington, D C, April 5 to 6, on "Possibilities for Pneumonia Control as Indicated by Present Scientific Knowledge".

Dr William H Walsh (Fellow), Chicago, addressed the Tri-State Hospital Assembly, sponsored by the hospital associations of Illinois, Indiana and Wisconsin, at Chicago May 5 to 7, on "Correct Designing of a Medical Record Library".

Dr Israel Davidsohn (Associate), Chicago, was a speaker at the annual banquet, sponsored by the Chicago Hospital Association, his subject being "Infectious Mononucleosis Its Hematologic and Serologic Diagnosis".

Dr Rafael Rodriguez Molina (Fellow), San Juan Puerto Rico, has been elected Secretary of the Puerto Rico chapter of the Pan American Medical Association.

Dr William R Brooksher (Fellow), Fort Smith, Ark, has been reelected Secretary of the Arkansas Medical Society for 1937 to 1938.

Dr George E Wakerlin (Fellow) has been appointed Professor and Head of the Department of Physiology at the University of Illinois College of Medicine, effective September 1. Dr Wakerlin has been Professor of Pharmacology and Physiology at the University of Louisville School of Medicine, Louisville, Ky.

Dr Ralph M Fellows (Fellow), Superintendent of the Osawatomie (Kan) State Hospital has been elected Vice-President of the Kansas Society for Mental Hygiene.

Dr Walter C Alvarez (Fellow), Rochester, Minn, addressed the seventieth annual session of the Mississippi State Medical Association at Meridian, Miss, May 11 to 13, on "Helpful Hints in the Diagnosis of Gastro-Intestinal Diseases"

Dr Clarence M Hyland (Fellow), Los Angeles, addressed the Nebraska State Medical Association at Omaha May 10 to 13, on "The Convalescent Serum Center and Its Value to the Community"

Dr Anton J Carlson (Fellow), Chicago spoke upon "Facts and Fallacies of Organotherapy" before the one hundred and forty-sixth annual meeting of the New Hampshire Medical Society at Manchester, May 18 to 19

Dr Meldrum K Wylder (Fellow), Albuquerque, has been appointed a member of the State Board of Public Health of New Mexico

Dr James C Walsh (Associate), Superintendent of the Schenectady (N Y) County Tuberculosis Hospital, has accepted an appointment as Superintendent of the Nassau County Sanatorium at Farmingdale, N Y

Dr Charles A Elliott (Fellow) Chicago, addressed the forty-fifth annual session of the Oklahoma State Medical Association at Tulsa, May 10 to 12, on "Management of Cardiovascular Disease, Management of Hepatic Disease" He also addressed the section on general medicine on "Management of Edema"

The Rhode Island Medical Society sponsored a series of lectures open to the public during the month of March Dr Charles F Gormly (Fellow), Providence, delivered one on the subject "How to Grow Old Gracefully" and Dr Henry L C Weyler (Associate), Providence, gave one on "Why Poison Yourself—The Nostrum Evil"

Dr Edgar A Hines (Fellow), Seneca, has been reelected Secretary of the South Carolina Medical Association for 1937 to 1938

Dr Malcolm T MacEachern (Fellow), Chicago, will address the fifth International Hospital Congress in Paris, July 5 to 12

Dr Harry S Bernton (Fellow), Professor of Hygiene, Georgetown University School of Medicine, Washington, D C, has been appointed clinical specialist in allergy in the bureau of chemistry and soils of the U S Department of Agriculture

Dr Porter P Vinson (Fellow), Richmond, Va, and Dr Charles Sidney Burwell (Fellow), Boston, Mass, were guest speakers on the program of the one hundred and forty-fifth annual meeting of the Connecticut State Medical Society at Bridgeport, May 19 to 20 Dr Vinson spoke on "Diagnosis and Treatment of Primary Malignant Disease of the Tracheobronchial Tree" and Dr Burwell's title was "Factors in the Treatment of Asymptomatic Period of Heart Disease"

Dr William B Castle (Fellow) Boston, and Dr Cyrus C Sturgis (Fellow), Ann Arbor, Mich, were guest speakers at the one hundred and thirty-first annual meeting of the Medical Society of the State of New York at Rochester, May 24 to 26

Dr Louis B McBrayer (Fellow), Southern Pines, has resigned as Secretary and Treasurer of the Medical Society of the State of North Carolina. He has been made honorary Secretary for life. Dr McBrayer served as President of the Medical Society of the State of North Carolina, and had been its Secretary and Treasurer for twenty-one years. The Society, in appreciation of his long service, gave a dinner in his honor, at which a silver service was presented. Dr Paul H Ringer (Fellow), Asheville, was toastmaster.

Dr Edward L Tuohy (Fellow and College Governor for Minnesota), Duluth, addressed the fiftieth annual session of the North Dakota State Medical Association at Grand Forks, May 16 to 18, and was the principal speaker at the annual banquet.

Dr Oscar B Biern (Fellow), Huntington, delivered the annual oration in medicine on "The Value of the Sedimentation Rate in Medicine" at the seventieth annual meeting of the West Virginia State Medical Association at Clarksburg, May 24 to 26. Other guest speakers included Dr Horton R Casparis (Fellow), Nashville, Tenn, "Mental Health of Children, Pediatric Responsibility in Health Education", Dr Louis F Bishop, Jr (Fellow), New York City, "Prevention of Heart Disease, Fugitive Arrhythmias", Dr Moses Paulson (Fellow), Baltimore, "Newer Aspects of Gallbladder Disease of Practical Import", and Dr Thomas Parran (Fellow), Surgeon General, U S Public Health Service, "Public Health Control of Syphilis".

Dr Edward S Sledge (Fellow), Mobile, was elected President of the Medical Association of the State of Alabama on April 22.

Dr John A Sevier (Fellow), Colorado Springs, is President of the Colorado Tuberculosis Association.

Dr William G Herrman (Fellow), Asbury Park, was installed as President of the Medical Society of New Jersey at its annual meeting in Atlantic City April 28.

Dr Rufus I Cole (Fellow), Director of Hospitals of the Rockefeller Institute for Medical Research, New York City, has been announced as the recipient of the George M Kober Medal by the Association of American Physicians for next year.

Dr Cole has announced that he will retire June 30, on account of age, as Director of the Hospital of the Rockefeller Institute for Medical Research. Dr Cole has been Director since 1909. He is a native of Rowsburg, Ohio, took his medical degree at Johns Hopkins University School of Medicine, 1899, and served in various capacities at Johns Hopkins Hospital from 1899 to 1907 and at the medical school from 1901 to 1909. He was President of the Association of American Physicians in 1931. He received the honorary degree of Doctor of Science from the University of Chicago in 1927. He has been a prolific contributor to medical literature and is a member of many national societies.

Dr Walter M Simpson (Fellow), Dayton, Ohio, was made a member of the Legion of Honor of France, in recognition of his research on artificial fever.

Dr Charles E Sears (Fellow), Portland, has been elected President of the Oregon State Medical Society for 1937 to 1938.

Dr William D Stroud (Fellow and Treasurer) was reelected President of the Philadelphia Heart Association, April 28 Dr Samuel A Levine (Fellow), Boston, was a guest speaker at the meeting and Dr David Riesman (Fellow), Philadelphia, as Chairman of the Executive Committee, reviewed the year's work

Dr William S Middleton (Fellow), Madison, Wis, has been appointed Chairman of the Council on Scientific Work of the State Medical Society of Wisconsin This committee supersedes the program committee

Dr William F Lorenz (Fellow), Madison, has been appointed Chairman by Governor La Follette of a "planning council" to develop a program for the control of venereal disease in Wisconsin

Dr Thomas Parran (Fellow), Surgeon General of the U S Public Health Service, gave as his Presidential Address "The Present Needs in the Public Health Control of Gonorrhea" before the American Neisserian Medical Society at Atlantic City, June 8

Under the Presidency of Dr Roy R Kracke (Fellow) Emory University, Ga, the American Society of Clinical Pathologists held its sixteenth annual meeting at Philadelphia, June 2 to 5 Dr Kracke's Presidential Address was on "The Future of Pathology"

Dr Jabez H Elliott (Fellow and College Governor for the Province of Ontario), Toronto, participated in a symposium on the evolution of tuberculosis dispensary control at the thirty-third annual meeting of the National Tuberculosis Association at Milwaukee, Wis, May 31 to June 3

OBITUARIES

DR OTIS SUMTER WARR

Dr Otis S Warr, a Fellow of the College, died in Knoxville, Tennessee, on March 22, 1937, of lobar pneumonia which developed while on a trip through the Great Smoky Mountain National Park

Dr Warr was born in Darlington, South Carolina, April 30, 1881 His preliminary educational advantages were those of the common school of his home community and later he attended the George Peabody College at Nashville, Tennessee He was graduated in medicine from the University of Nashville Medical College in 1907, and following this spent the next four years as intern in several hospitals including Bellevue Hospital in New York

At the conclusion of his internship Dr Warr pursued two years of post-graduate study at Harvard and in Vienna—his work in the latter city being interrupted by the outbreak of the World War On his return home he located in Memphis, Tennessee, where he soon became one of the outstanding internists With the entry of the United States in the World War his application for service in the U S Army was declined on physical grounds but being anxious as always to do his bit he devoted much time to service on one of the medical advisory boards

Early in his career Dr Warr became actively interested in medical organization work He became a Fellow of the College in 1920, was active in the formation of the Mid-South Post-Graduate Assembly held annually in Memphis At the time of his death he was President of the Memphis and Shelby County Medical Society For a number of years he served as Chairman of the Committee on Education of the Tennessee State Medical Association and it was due largely to his vision and energy and effort that the present two year program of Post-Graduate instruction in Obstetrics was provided for the rural practitioner throughout Tennessee

As a physician Dr Warr was outstanding—not only doing a large volume of private and consultation work but doing it unusually capably and well Early in his professional career he became connected with the Medical Department of the University of Tennessee and his ability as a clinical teacher was such that at the time of his death he had risen to the rank of Clinical Professor of Medicine A close student of the problems of diagnosis he was a frequent contributor to medical journals and to the programs of medical societies

But those who had the privilege of knowing Otis Warr will remember him not only as an excellent clinician and teacher but even more as a fine gentleman in whom courage, fairness, loyalty, kindness and sympathy were so outstanding that friendship and association with him were not only real pleasures but inspirations as well

J O MANIER, M D , F A C P ,
Governor for Tennessee

DR ISAAC SURNAMER

Dr Isaac Surnamer (Fellow), 345 Broadway, Paterson, N J, died April 23, 1937, of coronary thrombosis and cerebral hemorrhage, at the age of 64

Dr Surnamer was born in Riga, Latvia, formerly a part of Russia, October 25, 1872. He obtained his preliminary education in the Hildas Heimer Seminary in Berlin, Germany, and graduated from the Gymnasium at Berlin. From Berlin, he entered the Medical Department of the New York University from which he graduated as M D in 1896. In 1903, he took a post-graduate course in the clinics of Germany and in 1916 at Fordham University. He was consulting neurologist and psychologist at the Paterson General Hospital, the Paterson City Hospital and the Valley View Sanatorium for over 30 years, and was serving in that capacity at the time of his death. He was also Lecturer in Neurology at the Paterson General Hospital and the Hackensack General Hospital.

He was a member of the Passaic County Medical Society, the Medical Society of New Jersey, and a Fellow of the American Medical Association.

He was the first President of the Miriam Barnett Free School of Paterson, but was forced to resign several years ago because of declining health.

Dr Surnamer is survived by his wife, Anna Blumberg Surnamer, and two sons, Masso M. and Bertram S. Surnamer.

He was greatly beloved by his community and profession and those who knew him have suffered a great loss in his death.

CLARENCE L. ANDREWS,
Governor for New Jersey

DR EUGENE SMITH DALTON

Dr Eugene Smith Dalton died suddenly on April 19, 1937, of coronary thrombosis, at his home in Brooklyn, N Y, aged 55 years. Besides his wife, Jessie Brown Dalton, he is survived by a son, a daughter and one brother.

Receiving his early education in the public schools of Syracuse, N Y, he later entered Syracuse University and Syracuse Medical School, from which he obtained his medical degree in 1908. While in college, Dr Dalton was outstanding in athletics and an active member of the Psi U and Nu Sigma Nu Fraternities.

After the completion of his medical course, he interned at the City Hospital in New York City, where, under the training of such noteworthy teachers as Edward Janeway, Harlow Brooks, and Evan Evans, he acquired much of the thoughtful professional philosophy which characterized his career. Following this, and a year's residency at the Willard Parker Hospital for Contagious Diseases, he entered the practice of medicine in Brook-

lyn, N Y , devoting his attention almost from the beginning to the problems of internal medicine

Dr Dalton's professional career in Brooklyn could be looked upon as the ideal of medical success His ability and his professional influence grew steadily In his younger years he served as Attending Physician at the Kingston Avenue Hospital (for Contagious Diseases) and in 1916 was appointed Assistant Attending Physician at the Methodist Episcopal Hospital and became Attending Physician at the same institution ten years later Although never a prolific writer, Dr Dalton was an active participant in medical affairs and a ready commentator In addition to being a member of the A M A and the associated county and state societies, he was also a member of the Associated Physicians of Long Island, the Brooklyn Society of Internal Medicine, the American Heart Association and since 1929 a Fellow of the American College of Physicians In addition to his many medical associations, he was a member of the Flatbush Chamber of Commerce and for twenty-five years was an active Mason His favorite recreations consisted of hunting and fishing and, as a member of the Malone Fish and Game Club and the National Rifle Association of America, he was well known as an expert in these diversions

Dr Dalton was looked upon as a physician of unusually sound judgment, exacting and thorough in his methods Beyond this he was a man of broad sympathies, of unflagging devotion to duty and of compelling sincerity and intellectual honesty

The above information has been supplied by Dr Alexis T Mays, F A C P , a former associate of Dr Eugene Smith Dalton

C F TENNEY, M D , F A C P ,
Governor for Eastern New York

ABSTRACT OF THE MINUTES
ANNUAL BUSINESS MEETING
AMERICAN COLLEGE OF PHYSICIANS

ST LOUIS, APRIL 22, 1937

The Annual Business Meeting of the American College of Physicians was held at St Louis, April 22, 1937, with Dr Ernest B Bradley, President, presiding. Abstracted minutes of the preceding Annual Business Meeting held in Detroit, 1936, were read by the Executive Secretary, and by resolution approved.

President Bradley read the following report from the Board of Regents: "It is the feeling of the Regents that the standards for admission to the College should be progressively raised. A change in the By-Laws making certification by the American Board of Internal Medicine a prerequisite to Associateship was considered in recent months by the Board. It was felt, however, that this would at this time constitute too radical an increase in the requirements, and so this proposed amendment has been withdrawn. After further consideration, other proposals for increasing the standards will be submitted to the College.

"Another amendment discontinuing the admission to the College of physicians working in fields allied to internal medicine has likewise been withdrawn by the Regents. It is the present feeling of the Regents that the admission of a certain number of Fellows representing these allied specialties would be desirable. Any application for Fellowship in this class should be scrutinized with especial care and should ultimately require the certification of each candidate by his own special certifying Board or, lacking that, its equivalent in professional or scientific achievement."

Dr William D Stroud, Treasurer, presented the following report, which on resolution, was regularly approved:

TREASURER'S REPORT FOR 1936

"To the Members of the American College of Physicians

As of March 31, 1937, the College has invested securities of a book value amounting to \$101,857 00, of this amount \$58,853 00 is in the Endowment Fund, and \$43,004 00 is in the General Fund, \$82,250 00 or 80.75 per cent of the above amount is invested in bonds, \$4,741 00, or 4.65 per cent, is invested in preferred stocks, and \$14,866 00, or 14.6 per cent, is invested in common stocks. In addition, the College has in bank balances \$47,470 00, making a total of \$149,328 00, as compared with a total of \$157,329 00 approximately one year ago at the time of the last yearly meeting.

"Thus, you see in spite of purchasing our new home for \$52,500 00, and spending \$10,000 00 on furnishings and alterations, our total funds at the present time are only \$8,000 00 less than one year ago."

Mr E R Loveland, the Executive Secretary, made a brief report on the activities of his office, but omitted the statistical data customarily presented because these had been given by the President on the evening of the Convocation. The complete financial statements and auditor's report for 1936 follow these Minutes.

President Bradley, before laying down the gavel of office as President, thanked the members of the College, the Regents and the Governors for their cooperation, help and advice during his term of office

At this point, Dr James H Means of Boston was inducted as President Dr Means spoke at length concerning his aims during the coming year, and bespoke the help and advice of the members everywhere

Dr William Geiry Morgan, Secretary General, on behalf of the College, presented to Dr Ernest B Bradley, retiring President, a silver, engraved ferruled gavel "as a token of the profound appreciation of the rank and file of the College for the masterly way in which you have served as President" The gavel was accepted by Dr Bradley with an expression of appreciation and thanks

President Means, now occupying the chair, called for the report of the Committee on Nominations for 1937, which was presented, as follows, by Dr George Morris Piersol, Chairman

REPORT—COMMITTEE ON NOMINATIONS

For the Year 1937-38

A Nominations for the Elective Offices (already published in the March issue of the ANNALS OF INTERNAL MEDICINE as provided in the By-Laws)

<i>President-Elect</i>	William J Kerr, San Francisco, Calif
<i>First Vice-President</i>	David P Barr, St Louis, Mo
<i>Second Vice-President</i>	G Gill Richards, Salt Lake City, Utah
<i>Third Vice-President</i>	William Gerry Morgan, Washington, D C

B Nominations for the Board of Regents

Term Expiring 1939

Walter L Bierring, Des Moines, Iowa (to fill unexpired term of
Luther F Warren, deceased)

Term Expiring 1940

Ernest B Bradley, Lexington, Ky
Roger I Lee, Boston, Mass
Sydney R Miller, Baltimore, Md
Walter W Palmer, New York, N Y
O H Perry Pepper, Philadelphia, Pa

C Nominations for the Board of Governors

Term Expiring 1938

Francis G Blake, CONNECTICUT, New Haven (to fill unexpired term of
Henry F Stoll, deceased)
Harry L Arnold, HAWAII, Honolulu
John L Calene, SOUTH DAKOTA, Aberdeen

Term Expiring 1939

Hugh A Farris, MARITIME PROVINCES, St John, N B, Can

Term Expiring 1940

Fred W Wilkerson	ALABAMA, Montgomery
Fred G Holmes	ARIZONA, Phoenix
Lewis B Flinn	DELAWARE, Wilmington
Turner Z Cason	FLORIDA, Jacksonville
Glenville Giddings	GEORGIA, Atlanta
James G Carr	Northern ILLINOIS, Chicago
C W Dowden	KENTUCKY, Louisville
Edwin W Gehring	MAINE, Portland
Henry M Thomas, Jr	MARYLAND, Baltimore
G W F Rembert	MISSISSIPPI, Jackson
Louis H Fligman	MONTANA, Helena
LeRoy S Peters	NEW MEXICO, Albuquerque
Charles F Tenney	Eastern NEW YORK, New York
A B Brower	OHIO, Dayton
T Homer Coffen	OREGON, Portland
Charles T Stone	TEXAS, Galveston
Rock Sleyster	WISCONSIN, Wauwatosa
Ramon M Suarez	PUERTO RICO, San Juan
Fred Todd Cadham	MANITOBA, Winnipeg, Can

Respectfully submitted,

Committee on Nominations

WILLIAM B BRIED,

JAMES D BRUCE,

CHARLES T STONE,

CHARLES F MARTIN,

GEORGE MORRIS PIERSON, *Chairman*

After the receipt of the above report, Chairman Means called for nominations from the floor. None were made. Upon motion from the floor, duly seconded and regularly adopted, it was RESOLVED, that the nominations be closed. Whereupon Chairman Means declared all the candidates on the report of the Nominating Committee elected.

Upon motion by Dr. C W Dowden, seconded and carried, it was

RESOLVED, that the cordial thanks of the American College of Physicians be extended to the retiring President, Dr. Ernest B. Bradley, to the General Chairman, Dr. David P. Barr, and to the members of his committees, individually and collectively, for their faithful work in the preparation and conduct of the St. Louis Session, to the Ladies Entertainment Committee for their efficient and courteous entertainment of the visiting ladies, to the medical schools and hospitals of St. Louis for putting their facilities at the disposal of the College and for their helpful participation, to the Women's Auxiliary of the St. Louis Medical Society for providing automobiles, to the St. Louis Convention Bureau and its Director for their continuous and efficient assistance, and to the Jefferson Hotel and its Convention Manager for their cooperation.

Adjournment

Attest E. R. LOVELAND,
Executive Secretary

Elections of Secretary General and Treasurer

At a meeting of the Board of Regents at St. Louis on April 23, 1937, Dr. George Morris Piersol of Philadelphia was elected Secretary General, and Dr. William D. Stroud of Philadelphia was reelected Treasurer for 1937-38.

EXECUTIVE SECRETARY'S REPORT ON OPERATION

1936

The auditor's report of his examination of the accounts of the College is hereto attached. The statements disclose a continued improvement, as shown by the following:

1932 Surplus	\$ 10,598 08
1933 Surplus	5 801 06
1934 Surplus	16,160 07
1935 Surplus	17,182 09
1936 Surplus	24,948 53

The 1936 surplus was distributed as follows:

Endowment Fund	\$ 3,503 10
General Fund	21,445 43
	<u>\$ 24,948 53</u>

The total principal of the two Funds on December 31, 1936, was

Endowment Fund	\$ 61,784 82
General Fund	119,832 90
	<u>\$181,617 72</u>

One liquidating dividend of \$1,949 29 was received from the Bank of Pittsburgh, reducing the balance now in depositories of banks in hands of receivers to \$6 292 39.

A condensed comparison of income and expenditures for 1934, 1935 and 1936 appears on the following page. Only a Supplement to the 1935 Directory of the College was published during 1936 which accounts for the material decrease in this item over 1935, when a complete Directory was published.

The Executive Offices have been conducted conservatively, with expenditures held to a minimum for effective operation. The budgets for 1937 were approved by the Board of Regents December 13, 1936.

Respectfully submitted,

(Signed) E. R. LOVELAND,
Executive Secretary

January 1, 1937

A condensed comparison of income and expenditures for 1934, 1935 and 1936

General Fund

Income	1934	1935	1936
Annual Dues	\$20,875 35	\$21,569 88	\$23,070 95
Initiation Fees	6,142 32	9,479 50	11,455 00
Interest on Investments	3,117 89	1,852 54	2,358 02
Interest on Bank Balances	22 50		
Profit on Sale of Securities	1,178 39		1,077 04
Subscriptions, ANNALS OF INTERNAL MEDICINE	19,528 05	21,102 43	22,320 43
Advertising, ANNALS OF INTERNAL MEDICINE	4,455 28	5,353 89	6,014 06
Exhibits, Annual Clinical Session	6,124 85	12,361 02	6,291 04
Guest Fees, Annual Clinical Session	448 00	417 25	297 00
Miscellaneous Income	67 38	200 75	297 75
	<u>\$61,960 01</u>	<u>\$72,337 26</u>	<u>\$73,181 29</u>

Expenditures

Annual Clinical Session	\$11,646 40	\$14,139 26	\$ 9,975 84
ANNALS OF INTERNAL MEDICINE	19,216 05	21,373 02	23,667 54
Executive Secretary's Office	15,647 70	16,343 00	16,175 03
New College Headquarters, Maintenance, etc			1,381 64
1935 Directory		3,548 33	205 68
Loss on General Fund Investments Sold		149 63	
John Phillips Memorial Prize		840 26	*
Miscellaneous	624 79	703 39	983 10
	<u>\$47,134 94</u>	<u>\$57,096 89</u>	<u>\$52,388 83</u>

*Endowment Fund**Income*

Profit on Investments, sold and matured			\$ 418 10
Interest on Investments	\$ 2,311 63	\$ 2,115 79	2,242 21
Income from Cash in Savings Accounts		135 52	
Life Membership Fees	1,710 00	2,615 00	3,085 00
	<u>\$ 4,021 63</u>	<u>\$ 4,866 31</u>	<u>\$ 5,745 31</u>

Expenditures

*John Phillips Memorial Prize			\$ 75 13
Research Fellowship	\$ 450 00	\$ 2,250 00	1,514 11
Loss on Investments Called		53 28	
	<u>\$ 450 00</u>	<u>\$ 2,303 28</u>	<u>\$ 1,589 24</u>

H I MacLean,
309 Valley Road,
Llanerch, Pa

March 28, 1937

To the Board of Regents,
American College of Physicians, Inc.,
Philadelphia, Pa

Mr E R Loveland, Executive Secretary

Dear Sirs

I have examined the accounts of the

AMERICAN COLLEGE OF PHYSICIANS, INC

for the year ended December 31, 1936, and the accompanying statements, including the Balance Sheet at December 31, 1936, the analyses of the General Fund and the Endowment Fund, and the Detailed Statement of Operations for the year ended December 31, 1936, are in accordance with the books of account and in my opinion set forth correctly the financial position at December 31, 1936, and the results of operations for the calendar year ended December 31 1936, subject to the following comments

Cash The cash was properly accounted for The following is a statement of the cash in the various depositories

Girard Trust Company, Philadelphia	\$11,093 50
Provident Trust Company, Philadelphia	5,661 47
Royal Bank of Canada, Montreal	741 82
Philadelphia Saving Fund Society (Time Deposit)	2,648 37
Western Saving Fund Society (Time Deposit)	2,648 49
	<u>\$22,793 65</u>

The amount of cash in closed banks at January 1, 1936, was \$8,241 68, during the year a liquidating dividend amounting to \$1,949 29 was received, which reduced the amount to \$6,292 39, as shown by the following schedule

	<i>Balance Jan 1, 1936</i>	<i>Liquidating Dividend</i>	<i>Balance Dec 31, 1936</i>
Bank of Pittsburgh, Pittsburgh	\$3,411 26	\$1,949 29	\$1,461 97
Exchange National Bank, Pittsburgh	1,749 20		1,749 20
Highland National Bank, Pittsburgh	3,081 22		3,081 22
	<u>\$8,241 68</u>	<u>\$1,949 29</u>	<u>\$6,292 39</u>

Accounts Receivable The accounts receivable were examined and found to be less than one year old and appear to be good and collectible. The detailed accounts receivable were in agreement with the control account. The amount due from broker of \$2,180 31 represents the proceeds from the sale of 30 Shares of Steel Corporation of Canada, 7 per cent, preferred stock, and was confirmed by correspondence with Hornblower & Weeks. In accordance with the action of the Board of Regents, the amount advanced on account of expenses of the American Board of Internal Medicine has been recorded as an accounts receivable. No requests for confirmation of the other accounts were mailed.

Investments The securities were accounted for by direct correspondence with the Girard Trust Company of Philadelphia and the income for the period under review was verified. It is noted that the uninvested principal and income cash of the Endowment Fund has been segregated from the General Fund cash on the books of account of the College.

General The increase in the amount of the Endowment Fund and the General Fund during the year 1936 is as follows

	<i>Balance Dec 31 1935</i>	<i>Net Increase</i>	<i>Balance Dec 31, 1936</i>
Endowment Fund	\$ 58,281 72	\$ 3,503 10	\$ 61,784 82
General Fund	99,047 47	20,785 43	119,832 90
	<u>\$157,329 19</u>	<u>\$24,288 53</u>	<u>\$181,617 72</u>

In accordance with the instructions of the Executive Secretary, the prepaid insurance at December 31, 1936, was not set up as a deferred expense, the other deferred and accrued items were verified, the charges to the College Headquarters account were examined and included the amount paid for the property at 4200 Pine Street, settlement charges, alteration and improvement costs and other expenses incidental to preparing the property for occupancy, which in my opinion appear to be proper charges to this account, the charges to the Furniture and Equipment accounts represent proper additions to this account and the allowance for depreciation appears to be adequate, it is to be noted that no depreciation has been taken into account on the new equipment purchased for the new headquarters, inasmuch as these purchases occurred principally in November and December, no depreciation reserve has been set up on the new building, and the Executive Secretary has informed me that this problem is receiving the consideration of the Board of Regents, the footings and extensions of the inventory were verified, all ascertainable liabilities have been included in the balance sheet, all recorded receipts from dues, initiation fees, exhibits, advertising, sales of publications, etc., were properly deposited in bank and all disbursements, as indicated by the vouchers, cancelled checks and bank statements, were properly recorded in the books of account.

Very truly yours,

(Signed) H I MACLEAN,
Certified Public Accountant

1922

AMERICAN COLLEGE OF PHYSICIANS, INC

Balance Sheet, December 31, 1936

General Fund

Liabilities \$ 1,856 62

ANNUAL BUSINESS MEETING OF COLLEGE

Accounts Payable \$2,470 15
Deferred Income
Advance Session for Volumes XI
Annual Subscriptions for INTERNAL MEDICINE
and XII, ANNALS OF INTERNAL MEDICINE 345 16
2,815 31

119,832 90

General Fund, as annexed

\$124,504 83

\$ 61,784 82
596 44

Endowment Fund, Principal
Advance Account, Accrued Income due General Fund

\$ 62,381 26
\$186,886 09

TOTAL LIABILITIES

Assets

Cash in banks and on hand \$ 367 00
Accounts Receivable 2,180 31
Advertising 4,697 00
Due from Board of Internal Medicine 7,244 31
American College of Physicians, Inc. 169 40
Inventory of Keys, Pledges and Frames, at cost 127 08
Accrued Income on General Fund Investments 596 44
Accrued Income on Endowment Fund Investments 22,631 03
Investments at Book Value 555 00
Investment Deposits 2,299 50

6,292 39

57,343 70

8,452 40
2,862 98

\$124,504 83

Endowment Fund

\$ 1,337 09
596 44
60,447 73

\$ 62,381 26
\$186,886 09

Cash in banks
Accrued Interest
Investments at Book Value

TOTAL ASSETS

GENERAL FUND

For the Year Ended December 31, 1936

Balance, January 1, 1936	\$ 99,047 47
Less	
Transfer to Endowment Fund of the Initiation Fees of Life Members, net	660 00
	<u>\$ 98,387 47</u>

Summary of Operations for the Year ended December 31, 1936

Income

Annual Dues	\$23,070 95	
Subscriptions, ANNALS OF INTERNAL MEDICINE	22,320 43	
Advertising, ANNALS OF INTERNAL MEDICINE	6,014 06	
Initiation Fees	11,455 00	
Income from Invested Funds (General)	2,358 02	
Income from Endowment Fund (net)	652 97	
Exhibits, 20th Annual Session	6,291 04	
Guest Fees, 20th Annual Session	297 00	
Other Income	297 75	
Profit on Investments of General Fund sold (net)	1,077 04	\$73,834 26

Expenses

Salaries	\$18,629 69	
Postage, Telephone, Telegraph, etc	3,064 22	
Office Supplies and Stationery	1,030 92	
Printing	17,345 05	
Traveling Expenses	4 213 96	
Rent and Maintenance	2,845 99	
College Headquarters		
Maintenance	\$ 609 82	
Taxes	486 20	
Insurance	232 37	
Miscellaneous	53 25	1,381 64
Depreciation on Furniture and Equipment	393 10	
Other Expenses		
20th Annual Session	\$1,832 12	
ANNALS OF INTERNAL MEDICINE	212 95	
Miscellaneous	1,439 19	3,484 26
		<u>52,388 83</u>

Net Income for the Year Ended December 31, 1936 21,445 43

Balance, December 31, 1936 \$119,832 90

ENDOWMENT FUND

For the Year Ended December 31, 1936

Principal Account	
Balance, January 1, 1936	\$58,281 72
Add	
Life Membership Fees received during 1936	2,425 00
Transfer of Initiation Fees of New Life Members from General Fund, net	660 00
Profit on Investments, sold and matured	418 10
Balance, December 31, 1936	<u><u>\$61,784 82</u></u>

*Income Account

Income from Investments	\$ 2,242 21
Less	
Research Fellowship	\$1,514 11
John Phillips Memorial Prize	75 13
	<u>1,589 24</u>

Balance, Credited to General Fund for the period \$ 652 97

* At December 31, 1936, the accrued income included in the Income from Investments of the Endowment Fund amounted to \$596 44, and is due to the General Fund

DETAILED STATEMENT OF OPERATIONS
For the Year Ended December 31, 1936

<i>General Income</i>		
Annual Dues		\$23,070 95
Initiation Fees		11,455 00
Income from Endowment Fund (Net, after deducting Research Fellowship stipend and John Phillips Award)		652 97
Income from General Fund Investments		2,358 02
Profit from Sales of Keys, Pledges and Frames		30 53
Sales of 1935 Directory		13 30
Profit on Investments of General Fund sold (Net)		1,077 04
Dividend on Insurance Deposit		30 00
Gift of Equipment		218 00
		<u>\$38,905 81</u>

Twentieth Annual Session

<i>Expenses</i>		
Salaries	\$ 3,782 54	
Communications (Postage, Telephone, etc)	384 38	
Office Supplies and Stationery	148 76	
Printing	783 29	
Traveling Expenses	3,044 75	
Miscellaneous		
Advertising	\$ 67 62	
Badges	201 58	
Convocation and President's Reception	513 49	
Equipment Rental	100 00	
Ladies Committee	204 65	
Publicity and Reporting	196 00	
Smoker	398 03	
Other Miscellaneous Items	150 75	
	<u>1,832 12</u>	9,975 84

<i>Income</i>		
Exhibits (Net)	\$ 6,291 04	
Guest Fees	297 00	
Profit on Banquet	5 92	6,593 96
		<u>\$ 3,381 88</u>

Net Expenses of Clinical Session

Annals of Internal Medicine

<i>Income</i>		
Subscriptions		
Volume I	\$ 21 20	
Volume II	24 20	
Volume III	15 20	
Volume IV	20 48	
Volume V	16 80	
Volume VI	12 91	
Volume VII	24 91	
Volume VIII	81 70	
Volume IX	1,402 14	
Volume X	20,700 89	\$22,320 43

<i>Advertising (Net)</i>		
Volume IX	\$ 2,917 97	
Volume X	3,096 09	6,014 06
		<u>\$28,334 49</u>

<i>Expenses</i>		
Salaries	\$ 6,156 51	
Communications (Postage, Telephone, etc)	1,055 54	
Office Supplies and Stationery	402 00	
Printing	15,840 54	
Miscellaneous	135 78	
Allowances, Adjustments and Purchases	77 17	23,667 54

Net Profit on ANNAIS OF INTERNAL MEDICINE 4,666 95

Total Income \$43,572 76

Forward \$ 3,381 88 \$43,572 76

Brought Forward		\$ 3,381 88	\$43,572 76
<i>Executive Secretary's Office</i>			
Expenses			
Salaries	\$ 8,690 64		
Communications (Postage, Telephone, etc)	1,624 30		
Office Supplies and Stationery	480 16		
Printing	721 22		
Rent and Maintenance	2,845 99		
Traveling Expenses	1,169 21		
Fee to Custodian of Securities	130 17		
Loss on Foreign Exchange	8 75		
Miscellaneous Items	504 59	16,175 03	
<i>New College Headquarters</i>			
Maintenance	\$ 609 82		
Taxes	486 20		
Insurance	232 37		
Miscellaneous	53 25	1,381 64	
Investment Counsel Service		200 00	
ANNALS OF INTERNAL MEDICINE distributed Free to Life Members		390 00	
Depreciation on Furniture and Equipment		393 10	
Printing 1936 Supplement to 1935 Directory		205 68	22,127 33
Net Income for the Year Ended Dec 31, 1936			<u>\$21,445 43</u>

INVESTMENTS

December 31, 1936

<i>Par Value</i>	<i>Bonds</i>	<i>Endowment Fund Securities</i>	<i>General Fund Securities</i>	
\$ 5,000	Bell Telephone of Canada, 5s, 1955	\$ 5,562 50		
2,000	Canadian National (West Indies) SS Co., Ltd, 5s, 1955	2,040 00		
4,000	Chesapeake and Ohio RR, Series "D," 3½s, 1996	4,060 00		
5,000	Cities Service Co 5s, 1950		\$ 4,075 90	
1,000	City of Montreal, 5s, 1956	1,071 30		
5,000	Commonwealth Edison Co, First, Series "F," 4s, 1981	4,744 35		
5,000	Government of the Dominion of Canada, 4s, 1960	4,662 50		
2,000	Great Northern Railway Co, Series "H," 4s, 1946	2,100 45		
5,000	New York Central RR, 3½s, 1946	4,900 00		
5,000	Pennsylvania Railroad, Gen, 4¼s, Series "E," 1984		5,013 10	
2,000	Port of New York Authority, New York- New Jersey Interstate Bridge, 4½s, Series "B," 1952	2,042 20		
2,000	Port of New York Authority, New York- New Jersey Interstate Tunnel, 4¼s, Series "E," 1958	2,065 40		
5,000	Texas and Pacific Railway, Gen and Ref, B, 5s, 1977	5,313 40		
2,000	U S Treasury, 4s, 1954	1,998 13		
20,000	U S Treasury, 3½s, 1945	19,887 50		
<u>\$70,000</u>	<u>TOTAL s, Bonds</u>	<u>\$60,447 73</u>	<u>\$ 9,089 00</u>	<u>\$69,536 73</u>
<i>Shares</i>	<i>Stocks</i>			
50	General Motors Corporation		\$ 1,584 75	
45	Mid-Continent Petroleum Corporation		963 93	
70	National Breweries, Ltd		2,803 50	
20	J C Penny Co		1,375 30	
20	Standard Brands, Inc		2,467 50	
50	Timken Roller Bearing Company		3,407 25	
20	Union Carbide and Carbon Corporation		939 80	
	<u>TOTAL, Stocks</u>		<u>\$13,542 03</u>	
	<u>TOTAL, Investments</u>	<u>\$60,447 73</u>	<u>\$22,631 03</u>	<u>\$83,078 76</u>

ANNALS OF INTERNAL MEDICINE
Cost Analysis

	Number of pages			
	Scientific matter	News notes, Covers, etc	Paid advertising	Total
Volume I — July, 1927 to June, 1928	1040	151 ¹ ₄	10 ¹ ₄	1202
Volume II — July, 1928 to June, 1929	1195	254 ² ₂	98 ² ₂	1548
Volume III — July, 1929 to June, 1930	1133	248	163	1544
Volume IV — July, 1930 to June, 1931	1435	300	185	1920
Volume V — July, 1931 to June, 1932	1481	191	188	1860
Volume VI — July, 1932 to June, 1933	1582 ³ ₁	171 ¹ ₄	186	1940
Volume VII — July, 1933 to June, 1934	1517	137 ⁴ ₄	195 ³ ₄	1850
Volume VIII — July, 1934 to June, 1935	1597	149 ¹ ₄	193 ³ ₄	1940
Volume IX — July, 1935 to June, 1936	1708	157	241	2106
Average Circulation	Volume I — 1803 Volume II — 1999 Volume III — 2437 Volume IV — 2722 Volume V — 3090 Volume VI — 3134 Volume VII — 3173 Volume VIII — 3388 Volume IX — 3658			
	(Circulation, June, 1936, Issue—3,808)			

ANNALS OF INTERNAL MEDICINE—Cost Analysis—Continued

	Volume VII (11-30-36)	Volume VIII (11-30-36)	Volume IX (11-30-36)
<i>Income</i>			
Subscriptions (Net)	\$17,807 77	\$19,428 61	\$21,181 64
Advertising (Net)	<u>4,717 84</u>	<u>4,691 70</u>	<u>5,540 54</u>
	<u>\$22,525 61</u>	<u>\$24,120 31</u>	<u>\$26,722 18</u>
<i>Expenditures</i>			
Salaries	\$ 5,078 11	\$ 5,090 21	\$ 5,998 35
Communications (Postage, etc)	940 48	825 04	1,019 48
Office Supplies and Stationery	487 98	449 33	229 88
Printing	\$11,931 41	\$13,950 37	\$14,959 28
Less Repayment for Excess Illustrations			
Less Inventory of Stock	\$ 90 15	\$152 44	\$ 74 67
Traveling Expenses	<u>*100 00</u>	<u>*100 00</u>	<u>*200 00</u>
Miscellaneous	190 15	252 44	274 67
(Editor's Office, Copyright, etc)	<u>13 17</u>	<u>6 15</u>	<u>14,684 61</u>
	218 61	138 37	133 22
Surplus—Vol VII	<u>\$18,479 61</u>	<u>\$20,207 03</u>	<u>\$22,065 54</u>
	<u>4,046 00</u>	<u>3,913 28</u>	<u>4,656 64</u>
	<u>\$22,525 61</u>	<u>\$24,120 31</u>	<u>\$26,722 18</u>
		Surplus—Vol VIII	Surplus—Vol IX

* An arbitrary valuation determined from estimation of future sale value, and not on actual cost of printing

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